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Biomedical Entrepreneurship in U.S. Regions

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Abstract

Entrepreneurial ecosystem researchers generally focus on the few dominant factors affecting entrepreneurship. Insufficient attention has been paid to the interdependencies among regional conditions within an entrepreneurial ecosystem. We focus on the collective effects of factors for regional biomedical entrepreneurship. We use the fuzzy-set qualitative comparative analysis (fsQCA) method to identify sets of regional conditions promoting biomedical entrepreneurship in all 381 U.S. metropolitan areas. The results indicate three configurations contributing to high levels of regional biomedical entrepreneurship: the first one combines public sector biomedical R&D, biomedical patents, and human capital, thus stressing science conditions and related human capital; the second combines public sector biomedical R&D, biomedical patents, clinical trials, and venture capital, thus placing more emphasis on the regional infrastructure sustaining entrepreneurial activity; the third combines private sector biomedical R&D, biomedical patents, human capital, per capita income, population density, and venture capital, thus emphasizing the private sector's role on boosting regional biomedical entrepreneurship. There is no single recipe for a region to increase its level of biomedical entrepreneurship.

Keywords: biomedical, entrepreneurship, region, ecosystem, science, fsQCA
JEL Classifications: L26, R11, O32

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1. Introduction

What are the key factors of a vibrant entrepreneurial ecosystem? In this quest scholars and practitioners have proposed several factors for successful ecosystems (e.g., Feld, 2012; Isenberg, 2011; Kim, 2015; Mack & Mayer, 2016; Spigel, 2017; World Economic Forum, 2013). Long lists of factors have been identified by scholars and practitioners (Stam, 2015) including government support, human capital, financing system, accessible markets, cultural traits, existing firms, and so on.

Policymakers may encounter several challenges in the effort to apply best practices in their contexts. First, would factors singled out in a different location work well in my region? The question becomes relevant in light of the fact that each region has a different condition, development history, and characteristics (Edler & Fagerberg, 2017). A replicated policy may not work in a different environment even though it is considered an essential condition somewhere else. Second, are the factors identified somewhere else sufficient for my region? Policymakers need to consider the set of conditions that identify their regions. Third, what are the effective configurations of regional conditions leading to high levels of entrepreneurship? In this paper, we specifically focus on the biomedical entrepreneurial ecosystem.

We construct an analytical model designed to incorporate sets of regional conditions that promote biomedical entrepreneurship. The model is cognizant of the process of biomedical knowledge flows from scientific discoveries to several stages of clinical trials to sales and marketing. We posit that a successful biomedical business critically depends on 1) scientific knowledge, 2) commercialization capacity, 3) extant entrepreneurial base, and 4) supporting infrastructure. We extract ten key factors: public biomedical R&D, private biomedical R&D, the local presence of established large biomedical firms , translational research, biomedical patents,

clinical trials, per capita income, population density, , venture capital investment and human capital. We argue that these factors collectively contribute to the regional biomedical entrepreneurship as approximated by the number of the National Institutes of Health (NIH) Small Business Innovation Research (SBIR) program grants and venture capital deals. The data cover a period of ten years, from 2006 and 2015, and they have been collected from diverse sources including the NIH, National Science Foundation (NSF), U.S. Patent and Trademark Office, U.S. Census, U.S. Bureau of Economic Analysis, Pitchbook, and Compustat.

We use the fuzzy-set qualitative comparative analysis (fsQCA) in order to identify the configurations that are linked to high levels of biomedical entrepreneurship in all 381 U.S. metropolitan areas. Our conjecture is that different sets of conditions could lead to the same outcome, and that individual factors cannot decide the outcome since each condition could have a different effect on the others, depending on the often-complex development history and policies of a region.

Three pathways are identified to lead to high levels of biomedical entrepreneurship in a region. The first combines public biomedical R&D, biomedical patents, and human capital, thus stressing the conditions that promote scientific activities in the biomedical sector. The second combines public biomedical R&D, biomedical patents, clinical trials, and venture capital investment, thus placing more emphasis on the regional infrastructure that promote entrepreneurial activity. The third combines private sector biomedical R&D, biomedical patents, , per capita income, population density, venture capital investment, and human capital. There is no simple recipe for high levels of biomedical entrepreneurship, and a region does not need to have all conditions to have a vibrant biomedical sector. Public and private R&D in the

biomedical field, related patents, and venture capital investment rise as particularly important in promoting regional biomedical entrepreneurship.

The rest of the paper is organized as follows. Section 2 reviews the literature and presents the research questions. Section 3 introduces the analytical model while the methodology and data are presented in Section 4. Section 5 shows the analytical results. Finally, Section 6 discusses the results, touches upon policy implications, and concludes.

2. Literature Review and Research Questions

An entrepreneurial ecosystem is a dynamic system with diverse stakeholders, which can include entrepreneurs, universities, government, and consumers (Audretsch & Belitski, 2017). Each innovation system has different conditions, environments, and path dependencies (Edler & Fagerberg, 2017). For instance, both Silicon Valley and Boston have successful ecosystems, but their environments—especially their entrepreneurial cultures—and their development histories have been quite different (Saxenian, 1994). Scholars have paid significant attention to the underlying factors explaining the differences in regional economic activities (Brown & Mason, 2017; Feldman, 2014).

The entrepreneurial ecosystem approach is one of the conceptual tools to understand differences in regional economic activities by positioning entrepreneurs at the center (Brown & Mason, 2017). Definitions have proliferated. For instance, Audretsch and Belitski (2017) have stated that an entrepreneurial ecosystem is "a dynamic community of interdependent actors (entrepreneurs, suppliers, buyers, government, etc.) and system-level institutional, informational and socioeconomic contexts" (p. 1033). Stam (2015), more broadly, defined the entrepreneurial ecosystem as "a set of interdependent actors and factors coordinated in such a way that they

enable productive entrepreneurship" (p. 1765). The core elements include the interactions and collaborations among the players within a given system.

Based on the entrepreneurial ecosystem framework, researchers have proposed lists of conditions or attributes for a successful ecosystem (e.g., Acs et al., 2014; Feld, 2012; Isenberg, 2011; World Economic Forum, 2013). For instance, Isenberg (2011) suggested six central areas for a successful ecosystem: policy, finance, culture, support, human capital, and markets. These areas help explain how ecosystems work, and they also suggest the important ingredients for regional entrepreneurship. Other investigators have reported contributing factors for healthy ecosystem development. For example, Spigel (2017) found venture capital and the role of large tech firms as key factors for the success of Waterloo, Canada's entrepreneurial ecosystem. Transplanting this to an emerging economy environment, Fischer et al. (2018) indicate the importance of both centrifugal and centripetal conditions in determining the success of entrepreneurial ecosystems.

The interdependency among regional conditions within an ecosystem has not, however, been analyzed thoroughly (Stam, 2015; Stam & Van de Ven; 2021). First, some factors might only be effective or dominant under certain conditions and only in some specific regions (Spigel, 2017). The differential impact of factors might be due to the complex environment related to entrepreneurial activity or to different development stages of the system. For instance, venture capital might not be an essential element at the early stage of entrepreneurship, but it could become more important as firms grow (Mason & Brown, 2014). Second, there might be cases that produce similar outcomes in terms of entrepreneurship, even though they have different sets of regional conditions. Third, some of the variability is simply due to the difficulty in generalizing the results of extant research as a case study method is frequently employed

focusing on a single region to identify relevant factors for regional entrepreneurship (Feldman & Francis, 2003; Kim, 2015; Mack & Mayer, 2016; Spigel, 2017).

Another important aspect is the sectoral perspective of the entrepreneurial ecosystem. This view is especially important to discuss here because the present research focuses on the biomedical sector. The biotech sector has a distinguished anatomy, one that is quite different from other sectors including information technology (Pisano, 2006). Each sector has a unique set of actors, networks, institutions, and knowledge and technological foundations (Malerba, 2004). Thus, entrepreneurial ecosystems are based on industry-specific characters and characteristics (Mason & Brown, 2014). In a recent paper, Spigel (2022) summarizes the discussions on the ecosystem structure—"nested" and "cohesive" ecosystem, and empirically shows that FinTech industry in the UK has nested ecosystems. That is to say that the attributes needed for a successful entrepreneurial ecosystem like Silicon Valley may not be fully relevant to other sectoral innovation systems. It is necessary to consider the specific attributes associated with the sector under investigation.

Herein we address the following research question: What are the effective configurations of conditions associated with high levels of biomedical entrepreneurship in a region? Based on prior literature, we expect that a combination of factors can increase entrepreneurship, but that factor combinations will differ, at least partly, across regions.

3. Analytical Model

We propose an analytical model that allows us to investigate the sets of factors contributing to biomedical entrepreneurship in a region. Regions have different sets of conditions, reflecting their endowments, development paths, policies, organizations, customs,

and institutions. Do specific combinations of factors consistently generate better outcomes in terms of high levels of biomedical entrepreneurship?

The development process in the biomedical sector generally flows from scientific discoveries to several stages of clinical trials to sales and marketing (Fishburn, 2013; Pisano, 2006; Scherer, 2010). Universities and research institutions with public funding usually participate in the creation of knowledge for new drugs. On the other side of the spectrum, pharmaceutical companies focus their attention on near-market products, generally after the Phase I clinical trials stage (Fishburn, 2013). The area between basic research and near-market activities has been increasingly undertaken by biomedical firms and startups (Kettler, 2000; Pisano, 2006). The well-established business model of such biomedical firms is to license novel discoveries from universities, develop those discoveries further, and then sell the intellectual property rights or intermediate products to pharmaceutical companies (Pisano, 2006).

We construct our model by taking into account key factors for biomedical entrepreneurship at the regional level. We define biomedical entrepreneurship as knowledge-intensive entrepreneurial activities utilizing knowledge to exploit opportunities within biomedical field (Malerba & McKelvey, 2020; Pisano, 2006). As entrepreneurship is a localized phenomenon (Feldman, 2014; Stam, 2007), the regional contexts for biomedical entrepreneurship are also considered. We extract four key dimensions of regional factors that relate to the creation, development, and growth of the biomedical business: 1) scientific knowledge, 2) commercialization capacity, 3) extant entrepreneurial base, and 4) supporting infrastructure (See Figure 1). The first two dimensions reflect biomedical-specific characteristics while the remaining two dimensions are connected to the strength of the entrepreneurial ecosystem.

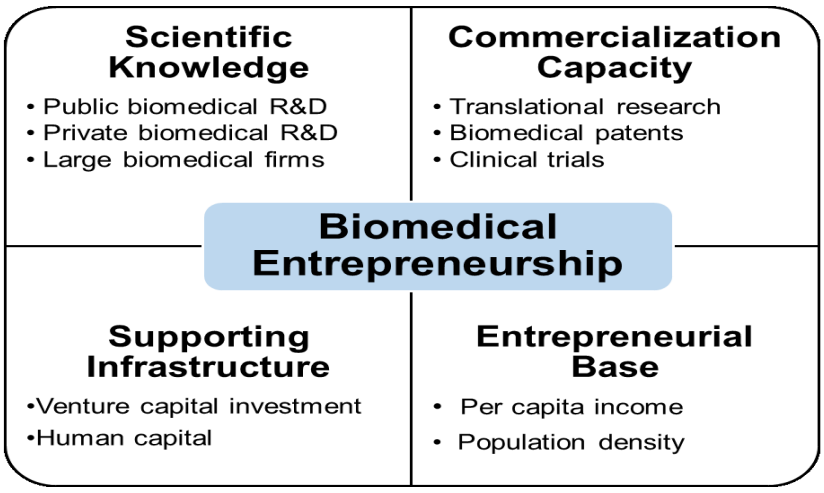

Figure 1. Schematic Description of the Model for Biomedical Entrepreneurship

Under this model, first, the biomedical entrepreneurial activity requires a source of scientific knowledge that can be developed further. Being a science-based business, its ability to create value depends on access to quality science. The roles of established firms are key, as they can provide positive externalities to nearby firms through complementary relationships (Audretsch, 2001; Kettler, 2000; Pisano, 2006; Scherer, 2010). Agrawal and Cockburn (2003) and Feldman (2003) proposed the anchor tenant hypothesis, which suggests that established R&D-intensive firms help the spread of research from local universities to regional firms. Based on this discussion, we suggest three factors for the scientific knowledge dimension in Figure 1: public biomedical R&D, private biomedical R&D, and the presence of established large biomedical firms.

Second, commercialization capacity is also important to transform scientific discoveries into commercially valuable properties. Not all novel scientific discoveries turn into useful, commercializable forms of knowledge (Braunerhjelm et al., 2010; Carlsson et al., 2009). A

higher capacity to commercialize knowledge in a region translates into both time reductions for the conversion of scientific knowledge and higher levels of economically exploitable knowledge. Strong capability in translational research could help produce more commercializable knowledge (like patents and clinical trials) available to biomedical entrepreneurs. Following this reasoning, we employ three factors for the commercialization capacity dimension of the model: translational research, biomedical patents, and clinical trials.

Third, it is also important to have favorable entrepreneurial conditions for an individual to start a business. Here, we consider two factors: per capita income and population density. Per capita income in a region might affect the conditions for starting a new business, as higher average income levels in a region could help support the starting of new businesses (Wallsten, 2001). Population density, which indicates the clustering of people in a region, can facilitate knowledge sharing and knowledge flow through close and frequent interactions (Qian et al., 2013).

Fourth, supporting infrastructure is also an important ingredient. Adequate funding is another critical area for biomedical firms to grow. The local venture financing system is important due to the large investment costs and the high degree of uncertainty involved in biomedical work (DiMasi et al., 2016; Pisano, 2006; Sacks et al., 2014). The availability of a trained labor force to generate and develop scientific knowledge is a prerequisite (Braunerhjelm et al.; 2010). Educated workers, such as newly graduating students and skilled researchers, bring their knowledge to the labor market, and this can result in knowledge spillovers without any formal distribution of knowledge. For the supporting infrastructure dimension of the model, we examine two factors: regional venture capital investment and human capital.

In sum, the model posits that biomedical entrepreneurship is a function of ten factors: public biomedical R&D, private biomedical R&D, the local presence of established large biomedical firms, translational research, biomedical patents, clinical trials, per capita income, population density, regional venture capital investment, and human capital.

4. Empirical Approach

4.1. Methodology: Fuzzy-set QCA

We employ fuzzy-set qualitative comparative analysis (fsQCA). The fsQCA method explores multiple paths that lead to the same outcome based on set-theoretical logic and the concept of equifinality (Kraus et al., 2018; Ragin, 2008). In other words, the main purpose of fsQCA analysis is to investigate how diverse conditions are combined for generating a particular outcome (Lee, 2014). The fsQCA approach has increasingly been used in entrepreneurship and management fields, including with research that has a large number of cases (Alves et al., 2021; Cooper & Glaesser, 2010; Kraus et al., 2018).

4.2. Data

The analysis runs at the level of the 381 U.S. metropolitan statistical areas (MSAs) as defined by the U.S. Office of Management and Budget (OMB). An MSA is defined as a region with "at least one urbanized area of 50,000 or more population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties" (U.S. Office of Management and Budget, 2018, p. 6).

Table 1 shows the utilized variables[1], corresponding measures, and data sources. The outcome is biomedical entrepreneurship, proxied by the National Institutes of Health (NIH) Small Business Innovation Research (SBIR) program grants. We obtained the NIH SBIR data from the NIH RePORTER (NIH, n.d.-a). The SBIR data include only new projects in Phase I and Fast Track because we focus on biomedical entrepreneurship, which is generally recognized by new firm formation (Lee et al., 2004; Qian et al., 2013).

We obtained regional public biomedical R&D spending from the National Science Foundation (NSF)'s Higher Education Research and Development (HERD) Survey (NSF, 2011, 2015, 2018). We aggregated the life science and medical R&D spending data in the universities at the MSA level. We collected the private sector's R&D spending on the biomedical field from Compustat, which is a collection of financial information of publicly-traded firms. We used the North American Industry Classification System (NAICS) codes[2] to select relevant biomedical firms as defined by DeVol et al. (2004). The number of large biomedical firms were also obtained from Compustat (2019).

Table 1. Variables, Measures, and Data Sources

Variable (abbreviation)		Measure	Data source
Outcome			
NIH SBIR grants **(Y)**		NIH SBIR (New projects in Phase I and Fast-Track) grants (counts)	NIH RePORTER
Dimensions	Conditions		
Scientific Knowledge	Public biomedical R&D (**R**)	R&D expenditure in the life science and medical field at the	NSF HERD Survey

[1] In this paper, we use the terms—variable, factor, and condition—interchangeably.

[2] NAICS (2017 version) codes used in this research: 325411, 325412, 325413, 325414, 339111, 339112, 339113, 339114, 339115, 339116, 335410, 335417, and 541714.

		universities (after subtracting the CTSA funding)	
	Private biomedical R&D (**P**)	R&D expenditure by publicly traded biomedical firms	Compustat
	Large biomedical firms (**L**)	Number of large biomedical firms belonging to the top 25% in annual revenue	Compustat
Commercialization Capacity	Translational research (**T**)	Average annual NIH CTSA program funding	NIH RePORTER
	Biomedical patents (**B**)	Number of patents in biomedical-related technology	U.S. PTO
	Clinical trials (**N**)	Number of clinical trials conducted	U.S. NLM
Entrepreneurial Base	Per capita income (**C**)	Per capita income	U.S. BEA
	Population Density (**A**)	Population per area (i.e., square miles)	U.S. Census
Supporting Infrastructure	Venture capital investment **(V)**	Regional venture capital investment	Pitchbook
	Human capital (**H**)	Percentage of adults (25+) holding a bachelor's degree or above	U.S. Census

Note. For all variables, we collected 10-year data between 2006 and 2015 and we use the average (mean) values to avoid fluctuations, following Alves et al. (2021).

We include the NIH's CTSA program funding by obtaining the data from the NIH RePORTER (NIH, n.d.-b) to measure the strength of translational research in a region. The data collection was based on the funding opportunity announcements (FOAs)[3] of the CTSA program to locate appropriate projects (Liu et al., 2016). We obtained biomedical patent data from the U.S. Patent and Trademark Office (PTO) (n.d.). Three technology fields—Class 424-Drug, Bio-Affecting, and Body Treating Compositions (includes Class 514); Class 435-Chemistry: Molecular Biology and Microbiology; and Class 800-Multicellular Living Organisms and

[3] The FOA numbers used in this research: RFA-RM-06-002, RFA-RM-07-007, RFA-RM-07-002, RFA-RM-07-006, RFA-RM-08-002, RFA-RM-09-004, RFA-RM-09-019, RFA-RM-10-001, RFA-RM-10-020, RFA-RR-10-007, RFA-RR-11-004, RFA-TR-12-006, RFA-TR-14-009.

Unmodified Parts Thereof and Related Processes—were selected based on Cortright and Mayer (2002). The patent data contains the granted utility patents between 2006 and 2015, the most recent year cataloged at the MSA level by the patent office. We collected the clinical trial data from the ClinicalTrials.gov website of the U.S. National Library of Medicine (NLM) (n.d.). Every clinical study has been registered in the depository by U.S. laws enacted in 1997 and 2007, and the International Committee of Medical Journal Editors' decision in 2005 (Califf et al., 2012). We first collected 180,926 clinical studies, based on the first study submission date from 2004 and 2015. We have 523,341 clinical trials conducted in the U.S. after cleaning study locations outside the U.S.

Per capita income data came from the U.S. Bureau of Economic Analysis (BEA) (n.d.). The data are to capture an individual's capacity in starting and supporting a new business, following Wallsten (2001) that utilizes per capita income in investigating the likelihood of winning the SBIR grants. We use population density following Qian et al. (2013) who use population density in estimating entrepreneurship in metropolitan areas as knowledge sharing and flow can be facilitated through close connections. The data were obtained from the U.S. Census Bureau (n.d.-b, n.d.-c). Regional venture capital investment data obtained from Pitchbook (2022), a data provider, were added to measure the strength of the regional venture financing. We proxy the human capital variable by the percentage of adults above 25 who hold at least a bachelor's degree following Florida (2002) and Qian et al. (2013). The data were collected from the U.S. Census Bureau (n.d.-a).

For all variables, we collected 10-year data between 2006 and 2015. We used the zip code-MSA code conversion file from the U.S. Department of Housing and Urban Development

(HUD) (n.d.) to aggregate the data at the MSA level. We use the average (mean) values to avoid fluctuations, following Alves et al. (2021).

4.3. Calibration

Based on Ragin (2008), we employ the direct calibration method, which applies three thresholds—full membership (1), full non-membership (0), and a crossover point (0.5). We use the percentiles of each condition to allocate three threshold points for membership status. This approach has been used by researchers, such as by Alves et al. (2021) and Greckhamer (2016). We choose the 1st percentile for full non-membership, the 99th percentile for full membership, and the 75th percentile as the crossover point[4]. Table 2 shows the thresholds for calibration used in this research.

Table 2. Thresholds for Calibration

Outcome / conditions	Full non-membership (0)	Crossover (0.5)	Full Membership (1)
SBIR grants (Y)	0.1	1.9	22
Public biomedical R&D (R)	0.006	111.178	1290.404
Private biomedical R&D (P)	0.005	72.011	7008.236
Large biomedical firms (L)	0.1	1.9	35.8
Translational research (T)	0.364	16.94	59.66
Biomedical patents (B)	0.1	12.8	447.1
Clinical trials (N)	0.5	99.58	1333.92
Per capita income (C)	26543.1	41102.3	67372.6
Population density (A)	14.5	343.09	2664.01

[4] For some conditions—SBIR grants, public biomedical R&D, private biomedical R&D, translational research, biomedical patents, large biomedical firms—that contain substantial portion of MSAs with zero values, the percentiles were calculated after removing the MSAs with zero values because these MSAs with zero values always fall below the full non-membership thresholds.

Venture capital investment (V)	0.003	24.77	4385.76
Human capital (H)	12.7	30.57	50.67

5. Analytical Results

Following the notation of Ragin and Fiss (2008) and Greckhamer (2016), we present the configurations constructed with a combination of intermediate and parsimonious solutions in Table 3. The analysis is conducted with fsQCA software by Ragin and Davey (2016). Following the recommendations from Ragin (2008) and Schneider and Wagemann (2012) to use a more substantial frequency threshold for large *N* (cases), we set the frequency threshold at 3, which means that we use configurations with more than three cases in the minimization process. It allows us to capture 85% of the cases, more than the recommend level of 75-80% by Ragin (2008).

The full circles and the crossed-out circles in Table 3 denote a condition's presence or absence, respectively. The large circles indicate core conditions observed in both the parsimonious and intermediate solutions, while the small circles denote complementary conditions observed in the parsimonious solutions but not in the intermediate solutions (Ragin & Fiss, 2008).

Table 3 shows that three configurations are linked to high levels of biomedical entrepreneurship. It represents three distinct configurations leading to high biomedical entrepreneurship in a region: Configuration 1, which focuses on accelerating scientific activities; Configuration 2, which has an emphasis on promoting entrepreneurial infrastructure conditions; and Configuration 3, which stress the role of private sector.

Table 3. Configurations for High Biomedical Entrepreneurship

Dimension / Condition	Configuration 1 (R*B*H)	Configuration 2 (R*B*N*V)	Configuration 3 (P*B*C*A*V*H)
Scientific Knowledge			
Public biomedical R&D (R)	●	●	
Private biomedical R&D (P)			●
Large biomedical firms (L)			
Commercialization Capacity			
Translational research (T)			
Biomedical patents (B)	●	●	●
Clinical trials (N)		•	
Entrepreneurial Base			
Per capita income (C)			•
Population density (A)			•
Supporting Infrastructure			
Venture capital investment (V)		●	●
Human capital (H)	•		•
MSA (Cases)	*Atlanta-Sandy Springs-Marietta (GA), Boston-Cambridge-Quincy (MA-NH), Chicago-Naperville-Joliet (IL-IN-WI), Minneapolis-St. Paul-Bloomington (MN-WI), New York-Northern New Jersey-Long Island (NY-NJ-PA), Philadelphia-Camden-Wilmington (PA-NJ-DE-MD), San Diego-Carlsbad-San Marcos (CA), San Francisco-Oakland-Fremont (CA), San Jose-Sunnyvale-Santa Clara (CA), Seattle-Tacoma-Bellevue (WA), Washington-Arlington-Alexandria (DC-VA-MD-WV)*		
	Baltimore-Towson (MD), Denver-Aurora (CO), Durham (NC)		
		Dallas-Fort Worth-Arlington (TX), Los Angeles-Long Beach-Santa Ana (CA)	
	Ann Arbor (MI), Columbus (OH), Gainesville (FL), Madison (WI), New Haven-Milford (CT), Worcester (MA)	Houston-Sugar Land-Baytown (TX), Miami-Fort Lauderdale-Pompano Beach (FL), Pittsburgh (PA), Salt Lake City (UT)	Austin-Round Rock (TX), Boulder (CO), Indianapolis-Carmel (IN), Oxnard-Thousand Oaks-Ventura (CA), Raleigh-Cary (NC), Trenton-Ewing (NJ)
Consistency	0.85	0.90	0.92
Raw Coverage	0.80	0.77	0.59
Unique Coverage	0.06	0.02	0.04
Solution Consistency	0.87		
Solution Coverage	0.83		

Note. ● = core causal condition present; ⊗ = core causal condition absent; • = complementary causal condition present; and ⊗ = complementary causal condition absent. MSAs in *italics* are common cases in three configurations.

Configuration 1 combines public biomedical R&D and biomedical patents as core conditions, along with human capital in complement. It indicates that regions featuring this combination of basic conditions can achieve high levels of biomedical entrepreneurship regardless of other conditions, such as private biomedical R&D, translational research, and large biomedical firms located in the region. Configuration 1 reflects the importance of scientific activities in the biomedical sector and is consistent with the literature emphasizing the role of science and human capital in the biotech business (Pisano, 2006; Zucker et al., 1998). Additionally, it sheds light on the core role of biomedical IPR (patents) in promoting biomedical entrepreneurship, in line with the knowledge spillover theory of entrepreneurship, which indicates that more knowledge production would lead to higher levels of entrepreneurship (Acs et al., 2009; Audretsch, 1995). Finally, this configuration stresses the importance of human capital as supporting infrastructure, thus in line with the literature (Braunerhjelm et al. 2010).

Configuration 2 combines the presence of public biomedical R&D and biomedical patents, and regional venture capital as core conditions, in combination with clinical trials as a complementary condition. The size of the regional venture investment reflects whether a region can provide the *sufficient* financial support such as through the market, the banking sector, or other sources of risk capital. The inclusion of clinical trials may reflect the concentration of infrastructural facilities (e.g., hospitals) that carry out clinical trials. While similar to Configuration 1 in terms of the core conditions, Configuration 2 differs in terms of the complementary condition, swapping human capital with clinical trials and regional venture capital investment. Configuration 2 thus places more emphasis on a strong regional infrastructure

that can support entrepreneurial activity.

Configuration 3 combines private sector biomedical R&D, biomedical patents, and regional venture capital investment as core conditions along with per capita income, population density, and human capital as complements. Interestingly, biomedical R&D by private firms appears in the configuration. This configuration, without the public biomedical R&D component, implies that regions with strong private firms conducting biomedical R&D may also have a vibrant biomedical ecosystem with other complements presented above. This inclusion of private firms' role may support the anchor tenant hypothesis by Agrawal and Cockburn (2003), and Feldman (2003), that suggest the extensive roles of the established firms. As Qian et al. (2013) have noted, population density can facilitate knowledge flow through the close and frequent interactions among potential entrepreneurs.

We have performed two robustness checks following the guidelines put forward by Schneider and Wagemann (2012) presented them in Appendix. The results show that the obtained three configurations are stable and that they are the supersets of the original solutions, as expected.

While we broadly define biomedical entrepreneurship (Malerba & McKelvey, 2020; Pisano, 2006) and use the number of SBIR grants for regional entrepreneurs as an approximation, more direct measurement for biomedical entrepreneurship could be considered. For this additional exercise, we use venture capital deal data (i.e., the number and dollar amount of deals) in the biomedical sector from Pitchbook as an alternative for the SBIR grants. The new measurement is more directly linked to the actual VC-backed biomedical startup activities in the region.

Following the same analytical procedure, we have one pathway leading to the vibrant biomedical entrepreneurial ecosystem: P (Private biomedical R&D) * B (Biomedical patents) * C (Per capita income) * A (Population density) * V (Venture capital investment) * H (Human capital). Table 4 shows the result. Interestingly, this configuration is one of three configurations that we've already had in the original analysis shown in Table 3. Thus, this exercise can also be regarded as an additional robustness check. The result also supports our proposition that vibrant regional biomedical entrepreneurship and business requires quite diverse sets of factors ranging from scientific inputs to the regional infrastructural conditions.

Table 4. Configuration with alternative dependent variable of biomedical VC deal

Path	Configurations	Raw Coverage	Unique Coverage	Consistency	Cases
1	P*B*C*A*V*H	0.75	0.75	0.85	19
	Solution Coverage	0.75			
	Solution Consistency	0.85			

6. Discussion and Concluding Remarks

The identification of three primary pathways for regional biomedical entrepreneurship engenders several significant implications. First, there is no single recipe for a region to increase its level of biomedical entrepreneurship. Second, a region does not necessarily need to possess all (ten) examined factors in order to have a vibrant biomedical business sector. It is also important that a region must assemble the proper set of conditions for success. Proper interaction between such conditions will generate the desired outcome. Third, a few core conditions are key for most of the pathways: public and private biomedical R&D, related IPR (patents), and venture capital. The three configurations emerging in the previous section, with their respective combined conditions, are sufficient to achieve high levels of biomedical entrepreneurship.

The emergence of these key factors is not surprising. As Pisano (2006) notes, biomedical enterprise is a science business, which requires new discoveries and ideas. New knowledge in the biomedical sector is generally generated from basic research largely funded by the public purse (NIH) or private firms. Patents in the biomedical sector are the channel for delivering the intellectual property from inventors to innovators, typically firms in the biomedical sector (Kettler, 2000; Pisano, 2006; Scherer, 2010). Strong venture capital infrastructure is also pointed out as a key ingredient for this resource-intensive and uncertainty-fraught biomedical business (DiMasi et al., 2016; Pisano, 2006; Sacks et al., 2014).

The presence of translational research turned out not to be an essential condition in our dataset. While when viewed in isolation translational research has been found to be a dominant factor affecting regional biomedical entrepreneurship (Park & Vonortas, 2022), the conjunctions of regional conditions can generate effective paths to biomedical entrepreneurship even in its absence. That said, this result should not be interpreted to mean that translational research is unimportant. Rather, it implies that translational research is not an *essential* element for biomedical entrepreneurship, since regions without the presence of translational research (or regardless participation in the CTSA program) can achieve high levels of biomedical entrepreneurship with the proper combination of other conditions.

The findings in this analysis can certainly inform regional policymakers. The first step for regional officers is to identify regional conditions before planning and implementing a biomedical entrepreneurship policy. Three different sets of conditions leading to vibrant biomedical activity in the region have been singled out herein. Public and private biomedical R&D, related IPR (patents), and venture capital infrastructure are key. Without their existence, little can be done in the region. Assuming reasonable presence, the regional officers need to

identify the supplementary conditions that will allow them to choose the pathway more relevant to their region. They may, then, embark on a more well-planned journey to acquiring them in order to achieve sustainable levels of biomedical entrepreneurship.

Regional policy to that effect should focus on increasing research capacities in the biomedical field. For instance, state governments could help research institutions by initiating research funding programs with emphasis on biomedical and life science fields. Furthermore, given that research in this high technology field depends heavily on sophisticated and large infrastructure, it might also be important to support regional research institutions obtain access to state-of-the-art facilities. Supporting activities for intellectual property protection in the biomedical field should also be in focus. Such support can come through various channels such as public awareness, IP identification, and legal and financial support.

We contribute to the literature in several fronts. First, using a relatively new empirical method—fuzzy-set QCA—in an ecosystem study with diverse sets of data, we explored the interdependencies of regional conditions that favor biomedical entrepreneurship.[5] We empirically identified three main pathways. Sharing main factors (i.e., public and private biomedical R&D, biomedical patents, venture capital) and supplementing them with different conditions reveals that a vibrant ecosystem would not be achieved by single policy recipe, but by an intertwined set of relevant measures. Importantly, all U.S. regions have been included in our analysis with micro data from different sources. Second, while informed by the extant literature, the chosen analytical approach allows "the data to speak" in some sense, that is it allows for emergent properties. Third, this study delved into entrepreneurship in the biomedical sector. As

[5] For a closely related exercise in an emerging economy setting see Alves et al. (2021). While somewhat different in terms of the set of examined factors, the tone of the results is quite similar to ours herein.

emphasized by prior literature, the biomedical business is science-based and quite different from other sectors. Our results confirm that the sector is strongly dependent on scientific knowledge as indicated by the emergent core conditions (i.e., public and private biomedical R&D spending, biomedical patents, and venture capital) and beyond. The results could inform the discussion on ecosystem structures such as nested and cohesive ecosystems.

In conclusion, we take note of the main limitation of this research and future extensions. We have utilized the NIH SBIR grants and venture capital deals to approximate regional biomedical entrepreneurship. This can be criticized as a narrow indicator, underestimating the real magnitude of entrepreneurship which should include all newly formed firms in the sector. In terms of coverage, the fsQCA method could be adopted in similar studies across different countries. One would have then additional tests of the said pathways that may or may not hold in different sets of regional conditions.

References

Acs, Z. J., Autio, E., & Szerb, L. (2014). National systems of entrepreneurship: Measurement issues and policy implications. *Research Policy*, *43*(3), 449–476. https://doi.org/10.1016/j.respol.2013.08.016

Acs, Z., Braunerhjelm, P., Audretsch, D., & Carlsson, B. (2009). The knowledge spillover theory of entrepreneurship. *Small Business Economics, 32*(1), 15-30. doi:10.1007/s11187-008-9157-3

Agrawal, A., & Cockburn, I. (2003). The anchor tenant hypothesis: Exploring the role of large, local, R&D-intensive firms in regional innovation systems. *International Journal of Industrial Organization, 21*(9), 1227-1253. doi:10.1016/S0167-7187(03)00081-X

Alves, A.C., Fischer, B. B., & Vonortas, N. S. (2021). Ecosystems of entrepreneurship: configurations and critical dimensions. *The Annals of Regional Science*, *67*(1), 73-106. https://doi.org/10.1007/s00168-020-01041-y

Audretsch, D. B. (1995). *Innovation and industry evolution*. MIT Press.

Audretsch, D. (2001). The role of small firms in U.S. biotechnology clusters. *Small Business Economics, 17*(1), 3-15. doi:10.1023/A:101114001433

Audretsch, D., & Belitski, M. (2017). Entrepreneurial ecosystems in cities: Establishing the framework conditions. *The Journal of Technology Transfer, 42*(5), 1030-1051. doi:10.1007/s10961-016-9473-8

Braunerhjelm, P., Acs, Z. J., Audretsch, D. B., & Carlsson, B. (2010). The missing link: Knowledge diffusion and entrepreneurship in endogenous growth. *Small Business Economics, 34*(2), 105–125. https://doi.org/10.1007/s11187-009-9235-1

Brown, R., & Mason, C. (2017). Looking inside the spiky bits: A critical review and conceptualization of entrepreneurial ecosystems. *Small Business Economics*, *49*(1), 11-30. doi:10.1007/s11187-017-9865-7

Califf, R. M., Zarin, D. A., Kramer, J. M., Sherman, R. E., Aberle, L. H., & Tasneem, A. (2012). Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *Jama, 307*(17), 1838-1847. doi:10.1001/jama.2012.3424

Carlsson, B., Acs, Z. J., Audretsch, D. B., & Braunerhjelm, P. (2009). Knowledge creation, entrepreneurship, and economic growth: A historical review. *Industrial and Corporate Change, 18*(6), 1193–1229. https://doi.org/10.1093/icc/dtp043

Compustat (2019). Fundamentals Annual. Retrieved from Wharton Research Data Service.

Cooper, B., & Glaesser, J. (2010). Using case-based approaches to analyse large datasets: A comparison of Ragin's fsQCA and fuzzy cluster analysis. *International Journal of Social Research Methodology, 14*(1), 31–48. https://doi.org/10.1080/13645579.2010.483079

Cortright, J., & Mayer, H. (2002). Signs of life: The growth of biotechnology centers in the US. The Brookings Institution Center on Urban and Metropolitan Policy.

DeVol, R., Wong, P., Ki, J., Bedroussian, A., & Koepp, R. (2004). *America's biotech and life science clusters: San Diego's position and economic contributions.* Milken Institute.

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics, 47*, 20-33. doi:10.1016/j.jhealeco.2016.01.012

Edler, J., & Fagerberg, J. (2017). Innovation policy: What, why, and how. *Oxford Review of Economic Policy, 33*(1), 2–23. https://doi.org/10.1093/oxrep/grx001

Feld, B. (2012). *Startup communities: Building an entrepreneurial ecosystem in your city.* John Wiley & Sons.

Feldman, M. (2003). The locational dynamics of the US biotech industry: Knowledge externalities and the anchor hypothesis. *Industry and Innovation, 10*(3), 311-329. doi:10.1080/1366271032000141661

Feldman, M. P. (2014). The character of innovative places: Entrepreneurial strategy, economic development, and prosperity. *Small Business Economics*, *43*(1), 9-20. https://doi.org/10.1007/s11187-014-9574-4

Feldman, M. P., & Francis, J. L. (2003). Fortune favours the prepared region: The case of entrepreneurship and the capitol region biotechnology cluster. *European Planning Studies, 11*(7), 765-788. doi:10.1080/0965431032000121337

Fischer, B. B., Queiroz, S., & Vonortas, N. S. (2018). On the location of knowledge-intensive entrepreneurship in developing countries: lessons from São Paulo, Brazil. *Entrepreneurship & Regional Development*, *30*(5-6), 612-638. https://doi.org/10.1080/08985626.2018.1438523

Fishburn, C. S. (2013). Translational research: The changing landscape of drug discovery. *Drug Discovery Today, 18*(9-10), 487-494. https://doi.org/10.1016/j.drudis.2012.12.002

Florida, R. (2002). The economic geography of talent. *Annals of the Association of American Geographers, 92*, 743–755.

Greckhamer, T. (2016). CEO compensation in relation to worker compensation across countries: The configurational impact of country-level institutions. *Strategic Management Journal, 37*(4), 793-815. https://doi.org/10.1002/smj.2370

Isenberg, D. J. (2011). The entrepreneurship ecosystem strategy as a new paradigm for economic policy: Principles for cultivating entrepreneurship. Retrieved from http://www.innovationamerica.us/images/stories/2011/The-entrepreneurship-ecosystem-strategy-for-economic-growth-policy-20110620183915.pdf

Kettler, H.E. (2000). Pharmaceutical and biotechnology industries coalescing. [Presentation at the American Enterprise Institute]. Washington, DC.

Kim, S. T. (2015). Regional advantage of cluster development: A case study of the San Diego biotechnology cluster. *European Planning Studies*, *23*(2), 238-261. https://doi.org/10.1080/09654313.2013.861807

Kraus, S., Ribeiro-Soriano, D., & Schüssler, M. (2018). Fuzzy-set qualitative comparative analysis (fsQCA) in entrepreneurship and innovation research: The rise of a method. *International Entrepreneurship and Management Journal, 14(*1), 15-33. doi:10.1007/ s11365-017-0461-8

Lee, S. S. Y. (2014). Using fuzzy-set qualitative comparative analysis. *Epidemiology and Health*, *36*. doi: 10.4178/epih/e2014038

Lee, S. Y., Florida, R., Acs, Z. J. (2004). Creativity and entrepreneurship: A regional analysis of new firm formation. *Regional Studies, 38*, 879–891. https://doi.org/10.1080/0034340042000280910

Liu, C., Xiao, L., Xu, R., Brazhnik, O. (2016). Assessing the public image of the NIH Clinical and Translational Science Awards (CTSA) program through analysis of publications. *2016 IEEE International Conference on Bioinformatics and Biomedicine (BIBM). Shenzen, China*.

Mack, E., & Mayer, H. (2016). The evolutionary dynamics of entrepreneurial ecosystems. *Urban Studies, 53*(10), 2118-2133. doi:10.1177/0042098015586547

Malerba, F. (Ed.). (2004). *Sectoral systems of innovation: Concepts, issues and analyses of six major sectors in Europe*. Cambridge University Press.

Malerba, F., & McKelvey, M. (2020). Knowledge-intensive innovative entrepreneurship integrating Schumpeter, evolutionary economics, and innovation systems. *Small Business Economics*, *54*(2), 503-522. https://doi.org/10.1007/s11187-018-0060-2

Mason, C., & Brown, R. (2014). Entrepreneurial ecosystems and growth oriented entrepreneurship. *Final Report to OECD, Paris*, *30*(1), 77-102.

National Institutes of Health (NIH). (n.d.-a). NIH RePORTER. Retrieved from https://projectreporter.nih.gov/reporter.cfm

National Institutes of Health (NIH). (n.d.-b). NIH RePORTER. Retrieved from https://projectreporter.nih.gov/reporter.cfm

National Science Foundation (NSF). (2011). Academic research and development expenditures: Fiscal year 2009. Retrieved from https://wayback.archive-it.org/5902/20181005000003/https://www.nsf.gov/statistics/nsf11313/content.cfm?pub_id=4065&id=2

National Science Foundation (NSF). (2015). Higher Education Research and Development Survey fiscal year 2014. Retrieved from https://ncsesdata.nsf.gov/herd/2013/

National Science Foundation (NSF). (2018). Higher Education Research and Development Survey fiscal year 2017. Retrieved from https://ncsesdata.nsf.gov/herd/2017/

Park, S. M. (2021). Positioning Translational Research in the Biomedical Ecosystem: from Basic Research to Biomedical Entrepreneurship (Doctoral dissertation, The George Washington University).

Park, S. M. & Vonortas, N. S. (2022). Translational research: from basic research to regional biomedical entrepreneurship. *Small Business Economics*. doi:10.1007/s11187-022-00676-9

Pisano, G. P. (2006). *Science business: The promise, the reality, and the future of biotech*. Harvard Business Press.

Pitchbook (2022). VC Deal Value by MSA. Retrieved from Pitchbook database.

Qian, H., Acs, Z. J., & Stough, R. R. (2013). Regional systems of entrepreneurship: The nexus of human capital, knowledge and new firm formation. *Journal of Economic Geography*, *13*(4), 559-587. https://doi.org/10.1093/jeg/lbs009

Ragin, C. (2008). *Redesigning social inquiry: Fuzzy sets and beyond*. University of Chicago.

Ragin, C. and Davey, S. (2016). Fuzzy-Set/Qualitative Comparative Analysis 3.0. Irvine, California: Department of Sociology, University of California.

Ragin, C., and Fiss, P. (2008). Net effects versus configurations: An empirical demonstration. In Charles Ragin (Ed.), *Redesigning social inquiry: Fuzzy sets and beyond* (pp. 190–212). University of Chicago Press.

Sacks, L. V., Shamsuddin, H. H., Yasinskaya, Y. I., Bouri, K., Lanthier, M. L., & Sherman, R. E. (2014). Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000-2012. *Jama, 311*(4), 378-384. doi:10.1001/jama.2013.282542

Saxenian, A. L. (1994). *Regional advantage: Culture and Competition in Silicon Valley and Route 128.* Harvard University Press.

Scherer, F. M. (2010). *Pharmaceutical innovation.* Elsevier B.V. doi:10.1016/S0169-7218(10)01012-9

Schneider, C. Q., & Wagemann, C. (2012). *Set-theoretic methods for the social sciences: A guide to qualitative comparative analysis*. Cambridge University Press.

Spigel, B. (2017). The Relational Organization of Entrepreneurial Ecosystems. *Entrepreneurship Theory and Practice, 41*(1), 49-72. https://doi.org/10.1111/etap.12167

Spigel, B. (2022). Examining the cohesiveness and nestedness entrepreneurial ecosystems: Evidence from British FinTechs. *Small Business Economics*, doi:10.1007/s11187-021-00589-z

Stam, E. (2007). Why butterflies don ‘t leave: Locational behavior of entrepreneurial firms. *Economic Geography*, *83*(1), 27-50. https://doi.org/10.1111/j.1944-8287.2007.tb00332.x

Stam, E. (2015). Entrepreneurial ecosystems and regional policy: A sympathetic critique. *European Planning Studies, 23*(9), 1759-1769. doi:10.1080/09654313.2015.106 1484

Stam, E., & Van de Ven, A. (2021). Entrepreneurial ecosystem elements. Small Business Economics, 56(2), 809-832. https://doi.org/10.1007/s11187-019-00270-6

U.S. Bureau of Economic Analysis (BEA). (n.d.). CAINC1 personal income summary: Personal income, population, per capita personal income. Retrieved from https://apps.bea.gov/iTable/iTable.cfm?reqid=70&step=1&isuri=1&acrdn=7#reqid=70&step=1&isuri=1&acrdn=7

U.S. Census Bureau. (n.d.-a). Educational attainment. Retrieved March 10, 2020, from factfinder.census.gov

U.S. Census Bureau. (n.d.-b). CBSA_est2018-alldata. Retrieved September 29, 2019, from https://www2.census.gov/programs-surveys/popest/datasets/2010-2018/metro/totals/

U.S. Census Bureau. (n.d.-c). CBSA report chapter 1 data: CBSAs. Retrieved September 16, 2019, from https://www2.census.gov/programs-surveys/decennial/tables/time-series/c2010sr-01/cbsa-report-chapter-1-data.xlsx

U.S. Department of Housing and Urban Development (HUD). (n.d.). HUD USPS zip code crosswalk files. Retrieved from https://www.huduser.gov/portal/datasets/usps_crosswalk.html

U.S. National Library of Medicine (NLM). (n.d.). Downloading contents for analysis. Retrieved from https://clinicaltrials.gov/ct2/resources/download

U.S. Office of Management and Budget (OMB). (2018). OMB bulletin no. 18-04: Revised delineations of metropolitan statistical areas, micropolitan statistical areas, and combined statistical areas, and guidance on uses of the delineations of these areas.

U.S. Patent Trademark Office (PTO). (n.d.). Patenting in U.S. metropolitan and micropolitan areas breakout by technology class. Retrieved September 30, 2019, from https://www.uspto.gov/web/offices/ac/ido/oeip/taf/cbsa_cls/index.html

Wallsten, S. J. (2001). An empirical test of geographic knowledge spillovers using geographic information systems and firm-level data. *Regional Science and Urban Economics, 31*(5), 571-599. https://doi.org/10.1016/S0166-0462(00)00074-0

World Economic Forum. (2013). Entrepreneurial ecosystems around the globe and company growth dynamics. World Economic Forum. Davos, Switzerland.

Zucker, L., Darby, M., & Brewer, M. (1998). Intellectual human capital and the birth of U.S. biotechnology enterprises. *The American Economic Review, 88*(1), 290. https://www.jstor.org/stable/116831

Appendix: Robustness Checks

We present two robustness checks following the guidelines by Schneider and Wagemann (2012).

First, following one of the suggested approaches, we lowered the consistency threshold to 0.78, which is the next highest consistency score. Schneider and Wagemann (2012) stated that the new solution becomes a superset of the original one when lowering the consistency threshold. Table 5 presents the new solution.

As expected, we have a new solution term with three configurations—public biomedical R&D (R)*human capital (H) + public biomedical R&D (R)*biomedical patents (B)*clinical trials (N)*venture capital investment (V) + private biomedical R&D (P)*human capital (H)*biomedical patents (B)*per capita income (C)*population density (A)*venture capital investment (V). Comparing them with the original solution terms found in Table 3, we see that the new solution terms are the supersets of the original intermediate solution terms. Thus, the first robustness check confirms the stability of the original solution terms.

Table 5. Solutions with a Lowered Consistency Threshold of 0.78

Path	Configurations	Raw Coverage	Unique Coverage	Consistency	Cases
1	R*H	0.83	0.08	0.80	20
2	R*B*N*V	0.77	0.02	0.90	20
3	P*H*B*C*A*V	0.59	0.04	0.92	19
	Solution Coverage	0.89			
	Solution Consistency	0.79			

Second, we changed the calibration of one condition—translational research. We utilize the presence of translational research funding, proxied by the NIH CTSA funding. To do so, we

put 46 MSAs with the CTSA funding over the cross-over point. Of the 46 CTSA-funded MSAs, we excluded two MSAs that received the funding in 2015, which is the last year of research period under review. Table 6 shows the new solution terms.

The new solution terms are virtually the same as the original one: public biomedical R&D (R)*human capital (H)*biomedical patents (B) + public biomedical R&D (R)* biomedical patents (B)*clinical trials (N)*population density (A)*venture capital investment (V) + private biomedical R&D (P)*human capital (H)*biomedical patents (B)*per capita income (C)*population density (A)*venture capital investment (V). One little change compared to the original solution terms is the addition of population density (A) in the second solution.

In sum, the two robustness checks demonstrate that the obtained configurations are stable and that they are the supersets of the original solutions as expected.

Table 6. Solutions with a Change in the Calibration of Translational Research

Path	Configurations	Raw Coverage	Unique Coverage	Consistency	Cases
1	R*H*B	0.80	0.11	0.85	20
2	R*B*N*A*V	0.71	0.02	0.90	20
3	P*H*B*C*A*V	0.58	0.04	0.92	19
	Solution Coverage	0.86			
	Solution Consistency	0.83			