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# Multi-scale network targeting: A holistic systems-biology approach to cancer treatment

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ABSTRACT

The vulnerabilities of cancer at the cellular and, recently, with the introduction of immunotherapy, at the tissue level, have been exploited with variable success. Evaluating the cancer system vulnerabilities at the organismic level through analysis of network topology and network dynamics can potentially predict novel anti-cancer drug targets directed at the macroscopic cancer networks. Theoretical work analyzing the properties and the vulnerabilities of the multi-scale network of cancer needs to go hand-in-hand with experimental research that uncovers the biological nature of the relevant networks and reveals new targetable vulnerabilities. It is our hope that attacking cancer on different spatial scales, in a concerted integrated approach, may present opportunities for novel ways to prevent treatment resistance.

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## 1. Introduction

Two basic complementary scientific approaches have been used to understand cancer. The first, the reductionist approach, focuses on the detailed description of the parts and subsequently tries to infer bottom-up, the functioning of the whole. The second one, the holistic approach, integrates top-down all the components and takes into consideration only certain features of the parts ignoring lower level details.

An example of the holistic approach is network analysis. In some contexts, organisms can be represented as complex embedded, multi-layered networks of interactions. Several levels can be identified, depending on the spatial scale of interest, see Fig. 1. At the cellular level, the networks are comprised of genes, different types of RNAs (i.e. miRNA, ltRNA), signaling molecules (proteins, lipids, ions, etc), and metabolic intermediates. At the tissue level, the networks are comprised of interactions between different cell types and between the cells and the supporting stroma. At the organismic level, the networks are comprised of interactions between different organs (heart, lung, etc) or different body systems (endocrine, nervous, immune, etc.). Networks interact with each other and we can think of two different broad classes of interactions: **horizontal interactions,** where the networks are located at the same level (for example, the interaction between the metabolic and genetic networks) and **vertical interactions,** where the networks are located at different levels (for example, cellular, tissue, and organismic). In general, networks interact and influence each other both horizontally and vertically.

## 2. Cancer networks

Networks, composed of various nodes and edges may be described at different levels in an organism. In a cancer cell, nodes may represent protein/RNA molecules or DNA-segments, where edges are their physical or signaling contacts. At the tissue levels, nodes can be the cancer cells and the stromal cells and the edges the different molecules through which they communicate. At the level of the whole organism, nodes may represent the different components of the cancer system and the different components of the normal body systems. Mathematical methods have been developed to study different aspects of networks, including dynamics of signaling on networks, birth-death and evolutionary processes on networks, and population dynamics on networks.

***Intracellular networks.*** The different intra-cellular networks of cancer cells, including protein–protein interaction, metabolic, signaling, and transcription-regulatory networks, contain thousands of nodes. Due to their high degree of complexity, a successful

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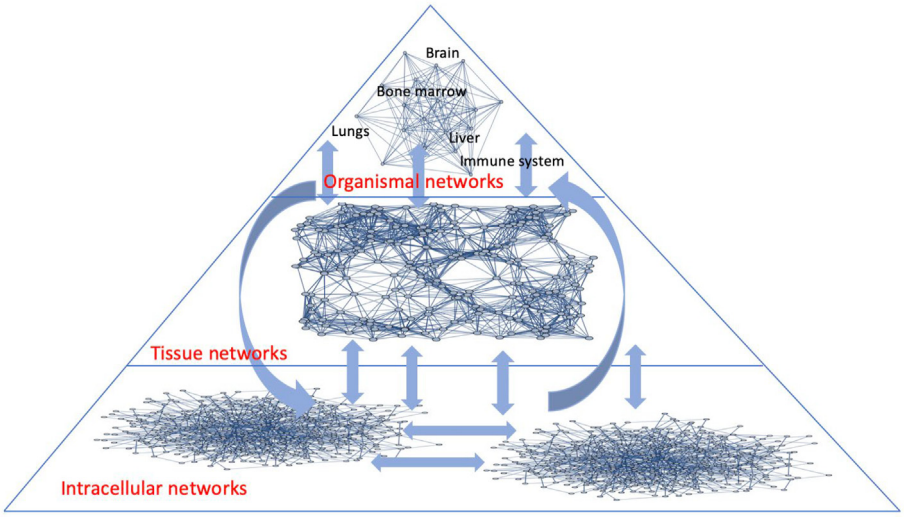


**Fig. 1.** A schematic of a multi-level network containing three scales of interest: intracellular, tissue, and organismic.

mathematical tool that has been used to study these interactions is the theory of random graphs. In particular it has been shown that the networks acting on the intracellular scales exhibit small-world or scale-free properties, and therefore their statistical properties can be studied by using methods developed for such abstractions as small-world or scale-free networks (Barabasi and Oltvai, 2004). The properties of intracellular networks have been carefully analyzed two decades ago (Tyson et al., 2003).

Regulatory gene networks and other intracellular networks have been shown to exhibit a number of highly conserved, specific patterns, or motifs (Boyle et al., 2014) that allow improved understanding of the biological function of healthy and cancerous cells.

Overall, the whole field of personalized oncology that subsequently evolved into the field of precision oncology started from the idea that idiosyncratic intra-cellular targets can be identified in each tumor and therapies can be developed against them. This approach was based on the concept that cancer cells are "addicted" to certain specific pathways associated with protein mutations or amplifications that can be targeted. The classifications of genetic alterations into "driver" and passenger" was also based on the idea that certain molecules "drive" the oncogenic process through an increase in cellular fitness, and others are just passive "passengers" that are either deleterious or do not provide fitness advantage. What became immediately apparent is that many of the oncogenic driver proteins are hyperconnected. The interactome of TP53 has at least 300 members (Collavin et al., 2010), EGFR at least 250 members (Li et al., 2013), etc. This hyperconnectivity and the existence of redundant networks that regulate interactions inside the cancer cells have been associated with the phenomenon of treatment resistance that has plagued the field of solid tumor cancer treatment using targeted small molecules (Sabnis and Bivona, 2019).

***Tissue networks.*** While most of network-related research in the last two decades focused on the intra-cellular level, tissue scales have received comparatively less attention in the context of network analysis. At the same time, it is becoming increasingly apparent that cell-to-cell communication and the influence of the microenvironment within organs play a very important role both in normal tissue functioning and in cancerous transformation (see e.g. Langley and Fidler, 2007; Forte et al., 2019; Burgos-Panadero et al., 2019).

One type of networks that has been the focus of our research in the last several years is the networks that govern cell-to-cell interactions on the tissue level (Armingol et al., 2021; Noël et al., 2021). Identifying the regulatory circuits that can stably maintain tissue homeostasis is critical not only for our basic understanding of multicellular organisms, but also for identifying how tumors circumvent this regulation, thus providing targets for treatment (Yuan et al., 2019; Dominiak et al., 2020). The main premise of our approach is to recognize that tissue consists of several types of cells that differ by their degree of differentiation. For example, cellular lineages could contain stem cells, intermediate (e.g. transit amplifying) cells, and terminally differentiated cells. Each of these cell types can potentially secrete regulatory factors and/or respond to factors secreted by other types. This gives rise to a specific formalism where the nodes of the network are different types of cells and the edges describe cell regulation, or feedback loops. These feedbacks can be positive or negative in nature, and control important cell fate decisions, such as cells' probability to divide, the type of division (including self-renewal, differentiation, asymmetric vs symmetric division, and de-differentiation), and death. Feedback loops are thought to be instrumental in maintaining the normal turnover of a lineage. It is however largely unknown what types of cells send and receive specific signals.

We have used mathematical modeling to address several types of questions related to the functioning of healthy tissues and cancer formation. This system of stochastically dividing and dying, hierarchically organized, communicating cells presents an interesting mathematical/engineering problem. What types of control networks are compatible with stability of the whole system? How large are fluctuations? How robust is the system to parameter changes? In several recent papers we developed a very general stochastic framework of describing the turnover of a complex, multi-compartment, multi-process system of stem cells and their lineages. This framework allows to analytically study the system's stability, the size of stochastic fluctuations, and the system's robustness. The emphasis is on the analysis of regulation networks and control that they exhibit.

In a series of recent publications, Komarova and colleagues developed an axiomatic theory of stem cell (SC) lineage dynamics, by modeling non-spatial (ODE) hierarchical dynamics and lineage regulation via nonlinear control loops. Assume that cells belong to a number of compartments of different degrees of differentiation. At the top of this hierarchy there are SCs that could engage in different types of cell divisions: (1) asymmetric divisions, whereby one of the

daughter cells retains its SC status and the other is moved to a more differentiated compartment; (2) symmetric self-renewal where both daughter cells are SCs, and (3) symmetric differentiations, where both daughter cells are more differentiated than the original cell. In a previous article, one of the authors (Komarova, 2013), under the assumption of symmetric SC divisions only, has characterized all the types of control networks that are compatible with stability, such that the number of control loops is minimal, see also Yang et al. (2015). In particular, there are some general principles according to which stable networks can be constructed, e.g. for minimal networks, the number of controls must be equal to the number of compartments, and each compartment must mediate a control. This analysis was extended in (Komarova and Driessche, 2018) for a more general set of deterministic systems. It was found that the reducibility/irreducibility of the network (whether or not it can be split into smaller independent sub-networks) is defined by a matrix comprised of the cell number increments induced by each of the controlled processes in each of the compartments. Using the formalism of digraphs, we classified general features of reducible and irreducible systems in 2- and 3-compartment systems and showed in what cases stability follows from the signs of the controls and does not require magnitude restrictions.

To give a specific example of a control system, assume two compartments, denoting the number of SCs by $x(t)$ and the number of differentiated cells (DCs) by $y(t)$. The different types of processes are listed in Table 1 with notations for the corresponding rates. The ODE model is given by

$$\dot{x} = x(-R+S) + yB,\ \dot{y} = x(2R+A) - y(D+B),$$

where in the most general case all the rates are functions of $x$ and $y$. Let us assume that a positive solution $x = \overline{x},\ y = \overline{y}$ of this system at steady state exists. These are exactly 10 minimal control networks in this case, see Fig. 2.

In previous work (Sun et al., 2016), Komarova and colleagues developed a near-equilibrium fluctuation analysis of hierarchical tissues for a stochastic system with an arbitrary number ($n$) of compartments. This framework allows one to calculate the means and variances of cell numbers for cell of different types within a lineage, as functions of the control loops that exist in the system. This methodology was used in (Yang et al., 2017), which focused on connecting theoretical results with the real biological observables (colon tissue). The exact regulatory network that governs stem cell lineages in a given tissue is usually unknown. Komarova and colleagues proposed an algorithm to identify a set of candidate control networks that are compatible with (a) measured means and variances of cell populations in different compartments, (b) qualitative information on cell population dynamics, such as the existence of local controls and oscillatory reaction of the system to population size perturbations, and (c) statistics of correlations between cell numbers in different compartments. Using the example of human colon crypts, where lineages are comprised of stem cells, transit amplifying cells, and differentiated cells, the authors started with a theoretically known set of 32 smallest control networks compatible with tissue stability. Utilizing near-equilibrium stochastic calculus of stem cells that Komarova and colleagues developed earlier, they applied a series of tests, where the networks' expected behavior was compared with the observations. This allowed to exclude most of the networks, until only three, very similar, candidate networks remained, which were most compatible with the measurements. This work demonstrated how theoretical analysis of control networks combined with only static biological data can shed light onto the inner workings of stem cell lineages, in the absence of direct experimental assessment of regulatory signaling mechanisms.

**Table 1**
Cellular processes and the corresponding per cell rate notations.

| Rate | Process |
|---|---|
| R(x,y) | Differentiation division of SCs |
| A(x,y) | Asymmetric division of SCs |
| B(x,y) | De-differentiation of DCs |
| $S_{SC}$, $S_{DC}$ | Self-renewal of SCs/DCs |
| $D_{SC}$, $D_{DC}$ | Death of SCs/DCs |
| S(x,y) | $S=S_{SC}-D_{SC}$ |
| D(x,y) | $D = D_{DC}-S_{DC}$ |

Mathematical tools described above can be applied to study cancer origins and progression in tissues. Cancers are thought to arise in tissue stem cells, and similar to healthy tissue, are thought to be maintained by a small population of tumor stem or initiating cells, the majority of tumor cells having a limited replicative potential. A key event in carcinogenesis is the escape from these feedback loops, see (Rodriguez-Brenes et al., 2011). By using ordinary differential equations that describe the co-dynamics of stem cells and differentiated cells, one can study the effect of different types of mutations that interfere with feedback present within cellular networks. In a recent study (Bailey and Komarova, 2021) investigate different types of mutations, and find that mutants that do not contribute to feedback signaling are less important in carcinogenesis, because they will remain at low numbers. On the other hand, mutants that "refuse" to respond to control signals could give rise to a wave of clonal expansion. The authors further studied different architectures of feedback networks, asking whether they may be characterized by different degrees of resilience against mutations. It was found that from an evolutionary prospective, redundant networks that combine multiple control loops are advantageous. On the other hand, from an engineering prospective, there may be subtle differences among such redundant systems, and depending on their exact architecture, some are more resilient against malignant transformations than others.

Applications of theoretical tools to study regulatory cell networks provide examples of network analysis that can aid in our understanding of cancer development on the intermediate, tissue levels. Another area of application is immunotherapy. Over the last decade, since the FDA approval of Ipilimumab (Ledford, 2011), immunotherapies with checkpoint inhibitors have improved the quality and duration of life of many cancer patients. As an example, the 4 year survival of melanoma has increased to approximately 50% by using a combination of nivolumab and ipilimumab (Larkin et al., 2019) and the overall 5 year survival of non-small cell lung cancer has more than doubled compared to historical data using check point inhibitors (Garon et al., 2019; Gettinger et al., 2018). We can argue that the success of the novel immunotherapy drugs as opposed to tyrosine kinase inhibitors is related to the fact that check point inhibition acts at the tissue level, blocking the brake put by the cancer cells on the immune cells and, by acting above the intracellular level on the communication between cancer cells and immune cells, are less affected by genetic heterogeneity than treatments targeting the cancer cells themselves. Also, cancer tissue networks have a simpler architecture with a smaller number of nodes due to the 3D geometric constrains of the stroma.

***Organismic networks.*** Finally, we turn to the largest scale considered here, which is the organismic scale a topic that has been the subject of a recent review article (Paul, 2020). Macroscopically, the integration of the organism into a functioning whole is realized, on one hand by a hierarchical architecture i.e. the existence of the neuroendocrine system that functions as a top-down cybernetic control system, and by the communication between the various organs established through the vascular and lymphatic circulatory

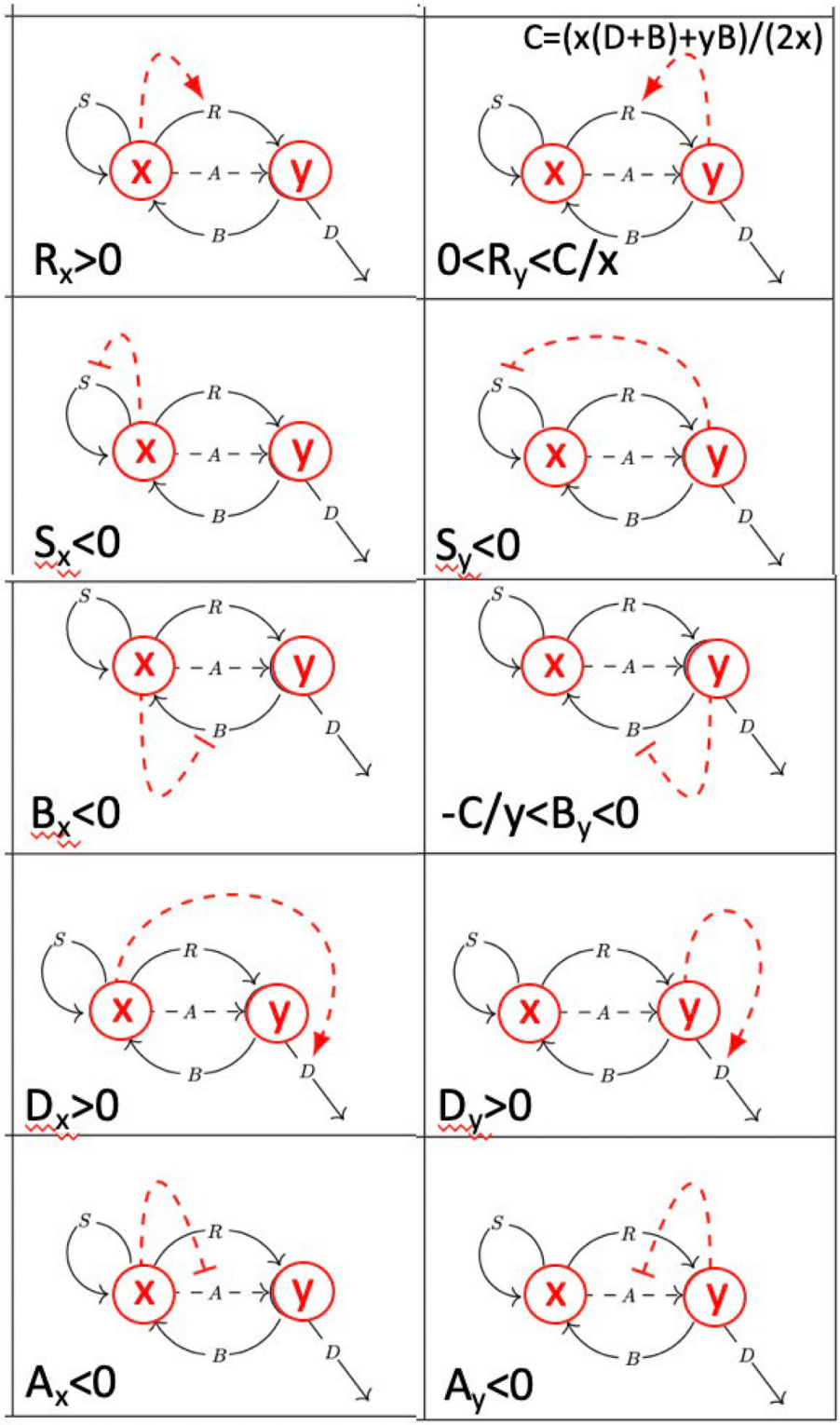


**Fig. 2.** Minimum control cases. The SCs and DCs are denoted by red x and y circles, black arrows represent the kinetic rates, and the red positive/negative arrows indicate control loops; they originate at the population that mediates control and point toward the process whose rate is being regulated. Subscripts refer to partial derivatives; all quantities evaluated at the equilibrium.

systems. Both the neuroendocrine system and the blood and lymph circulatory system are key components of the cancer networks at the organism scale. The neuroendocrine modulation of cancer progression is a well described phenomenon (Armaiz-Pena et al., 2009). The nervous system can also impact cancer development indirectly and the neuro regulation of the immune system described by Tracey (Tracey, 2007; Pavlov and Tracey, 2017) can be potentially exploited for therapeutic purposes.

Blood and lymph circulation are the communication routes that enable cancer to forge organismic networks. Cancer, either as a localized tissue in the initial stages, or, as several geographically separated tissues (the primary tumor, the local and the distant metastasis) in the metastatic stage, can be regarded as a system or a holobiont (Paul, 2021) that interacts through circulation with the normal body systems resulting in a "cancerized" organism (Paul, 2020). The pathologic networks induced by cancer at the organismic level are established through specific cellular (i.e. bone marrow derived macrophages), molecular (i.e. cytokines, metabolites) and, exosomal signals (McAllister and Weinberg, 2014; Wishart, 2019; Hoshino et al., 2020), by which the whole functionality of the organism is repurposed to serve cancer's agenda to grow and invade locally, and to disseminate at distance. Inter-organ communication in various acute and chronic medical conditions has been a hot topic of research in the last few years but formal mathematical analysis of networks at the organismic scale is almost completely missing from the literature and the cancer "circulome" databases are still in their infancy (Wu et al., 2020).

## 3. Three systemic therapeutic approaches

At the cellular and tissue level, cancer networks are able to maintain functionality despite various perturbations. At these levels, essential robustness of cancer is maintained through heterogeneous redundancy (Kitano, 2004, see also Mo et al., 2021), i.e., the cancer cells contain redundant survival pathways and the cancer tissue contains a heterogeneous distribution of genetically different cancer cells maintained by genetic instability. Kitano clearly specified that robustness is a global characteristic of the cancer system and not an individual characteristic of single cancer cells: "Even if each tumour cell is more fragile than a non-tumour cell in response to a particular chemotherapeutic drug, heterogeneous redundancy can give rise to robustness at the system level through genetic variability in the pattern of drug resistance" (Kitano, 2004).

Scale-free networks intracellularly are inherently robust, since nodes are connected by multiple different pathways. In a typical scale-free network, because of the existence of super-connected nodes, a large percentage of the links can be randomly destroyed before there is a catastrophic failure of complexity (Barabási and Oltvai, 2004). Similarly, in a cancer tissue, the majority of cells can be destroyed and the few remaining cancer cells are still able to grow new tumor colonies.

It is conceivable that treatments directed towards specific cancer induced pathologic networks at the organismic level, or at multiple levels simultaneously, would be associated with less resistance, as such treatments may allow exploring additional vulnerabilities of networks that are not accessible at the intracellular or tissue level alone.

Over the last decade it has been recognized the importance of organ to organ communication (Droujinine and Perrimon, 2013; Ivanov and Bartsch, 2014) in multiple acute i.e. sepsis (Ilaiwy et al., 2019) and chronic conditions like diabetes (Shirakawa et al., 2017), cardiovascular (Shalhoub et al., 2014), liver (Zhang et al., 2018) and kidney (Tatsumi et al., 2016) disease, immune disorders, degenerative disorders (Armutcu, 2019), including cancer cachexia (Argilés et al., 2018) and interaction between different organ networks at the organismic level is coming more in more into focus (Oishi and Manabe, 2020). The idea that cancer represents a distinct organ that interacts with the other body organs has been introduced for more than a decade (Egeblad and Nakasone, 2010). A Drosophila model for organ to organ communication has been developed in the lab of Norbert Perrimon (Droujinine and Perrimon, 2016, 2019). Several models of cancer as a systemic disease have been published (Edeblad et al., 2010; McAllister and Weinberg, 2010, 2014; Al-Zoughbi et al., 2014; Paul, 2015, 2020; Borniger, 2019).

Evaluating the cancer system vulnerabilities at the organismic level through analysis of network topology and, especially, network dynamics can potentially predict novel anti-cancer drug targets directed at the macroscopic cancer networks. Here we describe three possible directions.

### 3.1. Inhibiting the interaction between cancer and other organs (organism level, horizontal)

Given the non-scale free architecture of the cancer induced pathologic networks at the organismic level, treatments directed towards communication between cancer and key cancer supporting organs like the bone marrow or the liver, for example may be less plagued by resistance encountered by targeting intra-cellular or tissue networks (or at least, resistance mechanisms that exist at the lower levels, may no longer be relevant).

As has been demonstrated by the seminal work of David Lyden and his collaborators from Well Cornell (Kaplan et al., 2006), the formation of pre-metastatic niche is indispensable for the initial steps of metastasis. A treatment directed at the bone marrow derived macrophages that support the formation of the pre-metastatic niche, would drastically prevent the formation of metastasis. At the cellular level, the key metabolic pathway altered in cancer cells is the energy pathway. Also, arguably, the most important phenotypical characteristic of cancer tissue compared to normal tissues is an increased energetic need and targeting the interaction between cancer and various organs involved in the global energetic metabolism may be another modality of cancer treatment.

### 3.2. Top down treatments (vertical)

The brain is the central integration and supervision unit of the organism and all the major physiologic activities of the body are mapped and controlled by different central nervous system (CNS) and autonomous nervous system (ANS) modules (Wehrwein et al., 2016). We envision that in the near future, new drugs targeting neuroimmune (Huh and Veiga-Fernandez, 2020) and neuroendocrine (Procaccini et al., 2014) connections will be part of cancer armamentarium. The hypothalamus, for example, is a key structure involved in cachexia (Grossberg et al., 2010; Burfeind et al., 2016; van Noren et al., 2017) and, modulating the communication between hypothalamus and periphery may represent a novel therapeutic approach for this condition. As a proof of principle, amplifying a single gene in the hypothalamus of obese mice through gene transfer of brain-derived neurotrophic factor (BDNF) inhibited breast cancer progression and metastasis (Liu et al., 2014).

### 3.3. Multilevel networks targeting (vertical-horizontal)

In order to be able to dismantle such a complex multi-layered network as cancer, novel targeted multi-scale approaches are needed that target simultaneously key elements of the cellular, tissue and systemic cancer networks. Some agents, like beta blockers (Cole et al., 2015; Bucksek et al., 2017; Kokolus et al., 2018), or calcium channel blockers (Jacquemet et al., 2016; Wong et al., 2020), can target simultaneously organismic, tissue and cellular networks. Another multilevel network targeting example are diet interventions. Diet can modulate systemic inflammation through microbiota (Park et al., 2018) and can affect cancer grow (Xavier et al., 2020). A recent murine study demonstrated that in genetically engineered Apc-driven intestinal cancers and Myc-driven lymphomas, serine and glycine dietary restriction increased

survival (Maddocks et al., 2017). Also, in KRASG12A and NRASQ61K PDXs mouse models, methionine restriction significantly reduced tumor growth and increased the sensitivity to 5-fluorouracil, an inhibitor of pyrimidine nucleotide synthesis Gao et al. (2019). Crucially, the authors showed that dietary methionine restriction in a cohort of healthy humans also results in reduced levels of circulating methionine, cysteine and glutathione, comparable to the observations made in the murine models.

## 4. Discussion

In this paper we have reviewed recent paradigm-shifting advances in multiple areas of cancer research, which, taken together, suggest that holistic, system-biology approaches can be helpful in understanding cancer. Therefore, we have outlined tree possible directions, where the whole-organism scale enters as an important player. It is our hope that attacking cancer on different spatial scales, including the organismal scale, may present opportunities for novel ways to prevent treatment resistance.

Mathematically, different treatment strategies require different analysis tools and unique theoretical approaches. Of particular importance is multiscale modeling, which is notoriously difficult, computationally expensive, and hardly amenable to any analytical insights. Great strides have been made in the field of developing computational tools that allow numerical simulations of multiscale problems, see e.g. (Deisboeck et al., 2011; Marias et al., 2011). Another promising direction that can serve as a theoretical foundation of treatment strategies discussed here is the theory of multilayer networks (Boccaletti et al., 2014). Advances in biological understanding of the functioning of living organisms have inspired a surge in mathematical theory that introduced novel objects such as multiplex networks, interacting networks, and multidimensional networks. Multi-scale networks as such, however, have not been widely studied by bio-mathematicians, except perhaps some applications to neuroscience (see the review by Betzel and Bassett 2017).

Theoretical studies of network structure dynamics for multi-scale networks with given topological and statistical properties could provide useful tools to characterize the network vulnerability and address the problem of treatment resistance. For example, suppose a network has a scale-free structure at the lowest spatial scale, but starts resembling a spatial network in the intermediate (tissue) scales, while morphing into a relatively small but tightly-connected graph at the highest (organismal) level. How much can the scale-free properties observed at the intracellular level, influence the vulnerability of the whole object (Albert et al., 2000)? Can the error-tolerance of the scale-free graph that governs the key cancer drivers at the intracellular level be overridden, if one attacks top-down? Or, maybe, should we completely switch strategies and focus on strengthening the immune system at the organism level? What is the best approach to disrupt the network's integrity?

Even more ambitiously, the multi-scale of networks described here could be studied in the context of selection-mutation networks (Wodarz and Komarova 2014; Komarova and Wodarz 2014), bringing temporal and evolutionary angle to the framework.

Theoretical work analyzing the properties and the vulnerabilities of multi-scale network of cancer needs to go hand-in-hand with experimental research that uncovers the biological nature of the relevant networks and reveals possible intervention tools that may act at different scales.

## 5. Conclusion

It is time to zoom out from gene-centric and cellular centric paradigms of malignancy. Patients with advanced cancer are not killed by cancer genes or cancer cells but by changes induced by cancer at the organismic level. Introducing the organism factor in the cancer hyper-complex puzzle, may, in fact, help us solve it.

The model of cancer as a multidimensional spatio-temporal network with specific characteristics at the cellular, tissue and the organismic level that can be targeted through a combination of concerted multi-scale interventions may represent a paradigm shift that may guide the way we understand and treat cancer in the immediate future.

## Author statement

Doru Paul and Natalia L Komarova: conceptualization, research, manuscript writing (original draft) and manuscript review and editing.

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## Declaration of competing interest

The authors hereby declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

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