SOFTWARE TOOL ARTICLE

PressPurt: network sensitivity to press perturbations under interaction uncertainty [version 1; peer review: awaiting peer review]

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Abstract

While the use of networks to understand how complex systems respond to perturbations is pervasive across scientific disciplines, the uncertainty associated with estimates of pairwise interaction strengths (edge weights) remains rarely considered. Mischaracterizations of interaction strength can lead to qualitatively incorrect predictions regarding system responses as perturbations propagate through often counteracting direct and indirect effects.

Here, we introduce *PressPurt*, a computational package for identifying the interactions whose strengths must be estimated most accurately in order to produce robust predictions of a network's response to press perturbations. The package provides methods for calculating and visualizing these edge-specific sensitivities (tolerances) when uncertainty is associated to one or more edges according to a variety of different error distributions. The software requires the network to be represented as a numerical (quantitative or qualitative) Jacobian matrix evaluated at stable equilibrium.

PressPurt is open source under the MIT license and is available as both a Python package and an R package hosted at https://github.com/dkoslicki/PressPurt and on the CRAN repository https://CRAN.R-project.org/package=PressPurt.

Keywords

Press perturbation, sensitivity, loop analysis, uncertainty quantification

Open Peer Review

Approval Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the RPackage gateway.

This article is included in the Python collection.

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Introduction

Networks have become a routine tool for representing the complex systems that pervade biology, technology and society. While the development of methods for inferring network topology remains a dominant focus,[18,19,21-24] numerous methods are now also being advanced for quantifying the weights (fluxes and interaction strengths) of the edges between pairs of nodes (genes, metabolites, species) in different network types.[1,5,7,9,10] Motivating advances is the desire to predict how systems respond to perturbations wherein the concentration or process rates of a subset of nodes is chronically altered by external forces.[2,28] Examples of such perturbations include gene knock-downs, fisheries harvest, and the administering of antibiotics.[17,20,25,27]

Predictive insight into perturbation effects nevertheless remains hard to obtain. This is true even when a network's topology is fixed and precisely specified because edge weights are always subject to estimation error and empirical variation. Because of the many, often counteracting pathways through which perturbations travel, these uncertainties rapidly compound.[16,26] In many cases, therefore, predicting even just the qualitative sign pattern by which nodes respond to perturbations (i.e. whether concentrations increase, decrease, or remain unchanged) is of desirable interest.[6,14,17]

Here we introduce `PressPurt` – a collection of computational tools designed to shed light on the qualitative and quantitative response of a network to press perturbations when there is uncertainty in the magnitude of edge weights. The `PressPurt` package is written to implement in a usable form the theoretical results established in Ref. 11. `PressPurt` is designed to identify the most sensitive interactions within the network which must be estimated most accurately to produce robust predictions of press perturbation responses.

Methods

Scope

`PressPurt` is designed to analyze networks whose dynamics may be described by a system of differential equations of the form $\frac{dN_i}{dt} = f_i\left(\vec{N}\right) + u_i$ for $i = 1, \ldots, n$ variables. Here, $f_i\left(\vec{N}\right)$ is a function describing the interactions between node i and a vector of other nodes, N_i is node i's concentration, and u_i is a scalar representing a constant rate of external input to (or removal from) node i (a so-called *press perturbation*, sensu Ref. 2). Other forms of press perturbation may be represented in a similar manner.[17]

For input, `PressPurt` requires only a single CSV file representing the so-called Community Matrix[12]: the Jacobian of the system evaluated at a stable equilibrium point, $\left| A_{i,j} = \frac{\partial f_i\left(\vec{N}\right)}{\partial N_j} \right|_{x^*}$. `PressPurt` begins by determining how a press perturbation on each node j is predicted to alter the equilibrium concentration of each node i by calculating the Net Effects matrix without interaction strength uncertainty, $\frac{\partial N_i}{\partial u_j} = -A^{-1}_{ij}$.[6,17,26] Uncertainties in the elements of A that alter the sign structure of $-A^{-1}$ are the cause of qualitative mispredictions.[26]

Network sensitivity with single edge uncertainty

`PressPurt` can quantify the effects of interaction strength uncertainty in a single edge, independent of uncertainty in all other edges. To do so, the user specifies the kind of distribution and parameterization that describes interaction strength uncertainties. Currently, options include the uniform, truncated normal, truncated log normal, and beta distributions. Within the specified distribution, `PressPurt` finds the range of uncertainty values that permits the system to remain asymptotically stable, then returns a matrix in CSV format whose $(k,l)^{\text{th}}$ entry gives the expected (average) fraction of qualitative/sign changes in the net effects matrix resulting from the interaction uncertainty associated with edge (k,l). `PressPurt` can produce a visualization of the exact number of sign switches that are incurred as a function of uncertainty magnitude for a given edge (Figure 1b), as well as a heat map visualization of all edges depicting the fraction of possible sign switches that are incurred by uncertainty in each edge (Figure 1c). The overall sensitivity of the network when interaction uncertainty is considered one edge at a time is also returned as a percent of all n^2 possible mispredictions.

Similar computation and visualization functions are provided to measure the quantitative response of the network when interaction strength uncertainties are at their stability-limited values. In this context the actual magnitude change in the net effects matrix is computed, as opposed to just quantifying sign-changes in the net effects matrix.

Network sensitivity with multiple edge uncertainty

`PressPurt` can also quantify the effects of interaction strength uncertainty when it is associated with multiple edges simultaneously. This is achieved via Monte Carlo sampling where uncertainties are presumed to follow a uniform distribution of a user-specified length. The fraction of samples that contain a qualitative misprediction in the net effects matrix is then reported.

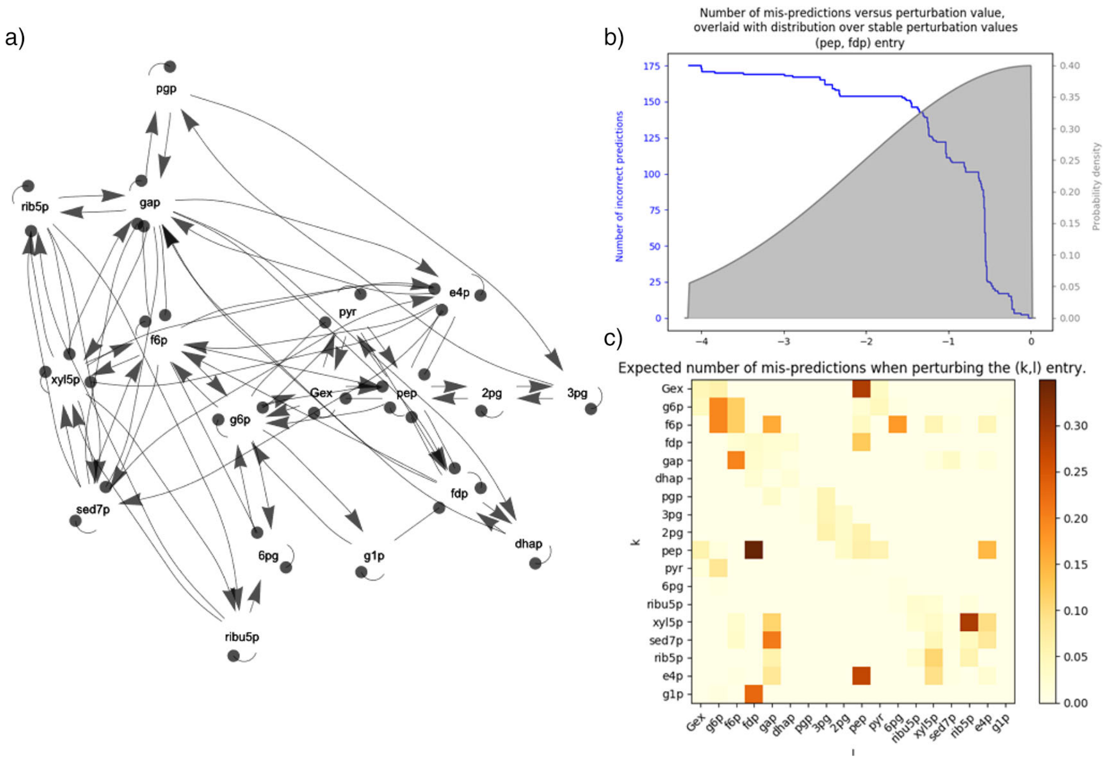

Figure 1. We demonstrate the `PressPurt` package on the *Escherichia coli* metabolic network inferred by Ref. 3 and quantified in Jacobian form by Ref. 10. Panel a) shows the network with positive and negative interactions depicted with arrowheads and balls respectively. Panel b) shows how uncertainty in the magnitude of the (pep, fdp) interaction (assuming a truncated normal uncertainty distribution, shown in gray) affects the number of qualitative mispredictions (sign changes in the net effects matrix, shown in blue) that are made regarding how the concentrations of the network's metabolites will respond to press perturbations. Panel c) shows a heat map of the expected (average) fraction of mispredictions that are incurred by uncertainty in each (*k*, *l*) edge (i.e. for the (pep, fdp) edge, the integration of the blue line with respect to the gray distribution in panel b). It demonstrates that uncertainty in the direct effect of fructose-1,6-bisphosphate (fdp) on phosphoenolpyruvate (pep) will result, on average, in the most mispredictions in the net effects of a unit perturbation to any of the metabolites in the network).

Implementation

`PressPurt` is available as both a Python package and an R package hosted at `https://github.com/dkoslicki/PressPurt` and on the CRAN repository `https://CRAN.R-project.org/package=PressPurt`. These provide complete documentation of all functions, as well as detailed installation instructions, quick start and use tutorials with example data (i.e. Jacobian matrices).

Operation

The `PressPurt` Python package is dependent on the Python packages *numpy, scipy, matplotlib, sympy, pathos* and *pandas.* The `PressPurt` R package is dependent on Python for its symbolic toolbox and uses the R package *reticulate* to communicate with Python. Thus Python, as well as its dependent packages, must be installed. It also depends on the R packages *data.table, ggplot2, grid, gridExtra* and *utils*, primarily for the convenience of their efficient data manipulation and visualization functions.

Use case

For input, `PressPurt` requires only a single CSV file representing either a quantitative or qualitatively-specified Jacobian matrix and the specification of a desired error distribution for the edge weight uncertainties. The three steps of an analysis entail: (1) preprocessing the Jacobian matrix, (2) computing the entry-wise or multi-entry perturbation expectations for either qualitative or quantitative sensitivities, and (3) visualizing the results. In R, for example, determining and visualizing the qualitative entry-wise sensitivities of a four-species intraguild predation module (whose Jacobian matrix[11]

$$\begin{bmatrix} -0.237 & -1.000 & 0.000 & 0.000 \\ 0.100 & -0.015 & -1.000 & -1.000 \\ 0.000 & 0.100 & -0.015 & -1.000 \\ 0.000 & 0.045 & 0.100 & -0.015 \end{bmatrix}$$

is provided in `PressPurt` as IGP.csv) involves three commands. First,

```
infile <- system.file("extdata", "Modules", "IGP.csv",
                        package = "PressPurt")
PreProsMatrix <- PreprocessMatrix (input_file = infile
                                   max_bound = 10,
                                   zero_perturb = FALSE,
                                   threads = 2)
```

which returns information that includes, for each non-zero edge, their asymptotic stability intervals and values that would lead to a sign switch in the net effects matrix. Second,

```
Entrywise <- ComputeEntryWisePerturbationExpectation (
                          PreProsMatrix = PreProsMatrix,
                          distribution_type = "truncnorm",
                          input_a = 0, input_b = -2, threads = 1)
```

which specifies a truncated normal distribution of edge weight uncertainties with mean 0 and variance 2 (a negative value indicates that the standard deviation is to be the scaled to each edge weight) and whose output includes a matrix containing the consequent expected number of sign switches in the net effects matrix expressed as a percentage of all 16 possible mispredictions,

$$\begin{bmatrix} 0.03 & 0.06 & 0.00 & 0.00 \\ 0.06 & 0.12 & 0.05 & 0.02 \\ 0.00 & 0.03 & 0.16 & 0.01 \\ 0.00 & 0.05 & 0.08 & 0.17 \end{bmatrix}.$$

Third,

```
GenerateEntryWiseFigures (EntryWise = Entrywise,
                          all_numswitch_plots = TRUE)
```

which produces Figure 2 that overlays visualizations of the assumed uncertainty distribution associated with each edge weight and the consequent number of qualitative mispredictions (sign switches) that a given magnitude of edge weight uncertainty will incur in the net effects matrix as a whole.

Summary

The measures of sensitivity that `PressPurt` implements are exact and may be computed with relative ease and computational efficiency. `PressPurt` thereby obviates the need for what are typically computationally expensive simulations whose results can be difficult to interpret when assessing the sources of mispredictions in complex networks. Underlying these advances is the separation of uncertainty magnitudes from their frequency distributions (Figure 1b). Moreover, the theorems of Ref. 11 show that the analysis of qualitative models via Loop Analysis[13] – the most commonly applied tool in context of fisheries management and conservation science wherein the values of A are specified as either -1, 0, or 1 – are a special case of the methods implemented in `PressPurt`. In this regard, `PressPurt` complements the functionality of other network-based packages such as Refs. 4, 8, 15.

Future extensions of `PressPurt` may include reformulating the code to: (1) compute which predictions in the net effects matrix are most sensitive to errors in focal (or multiple) entries of the Jacobian, (2) determine which interactions are most sensitive with respect to a specific net effects prediction, and (3) allow for different kinds of distributions or

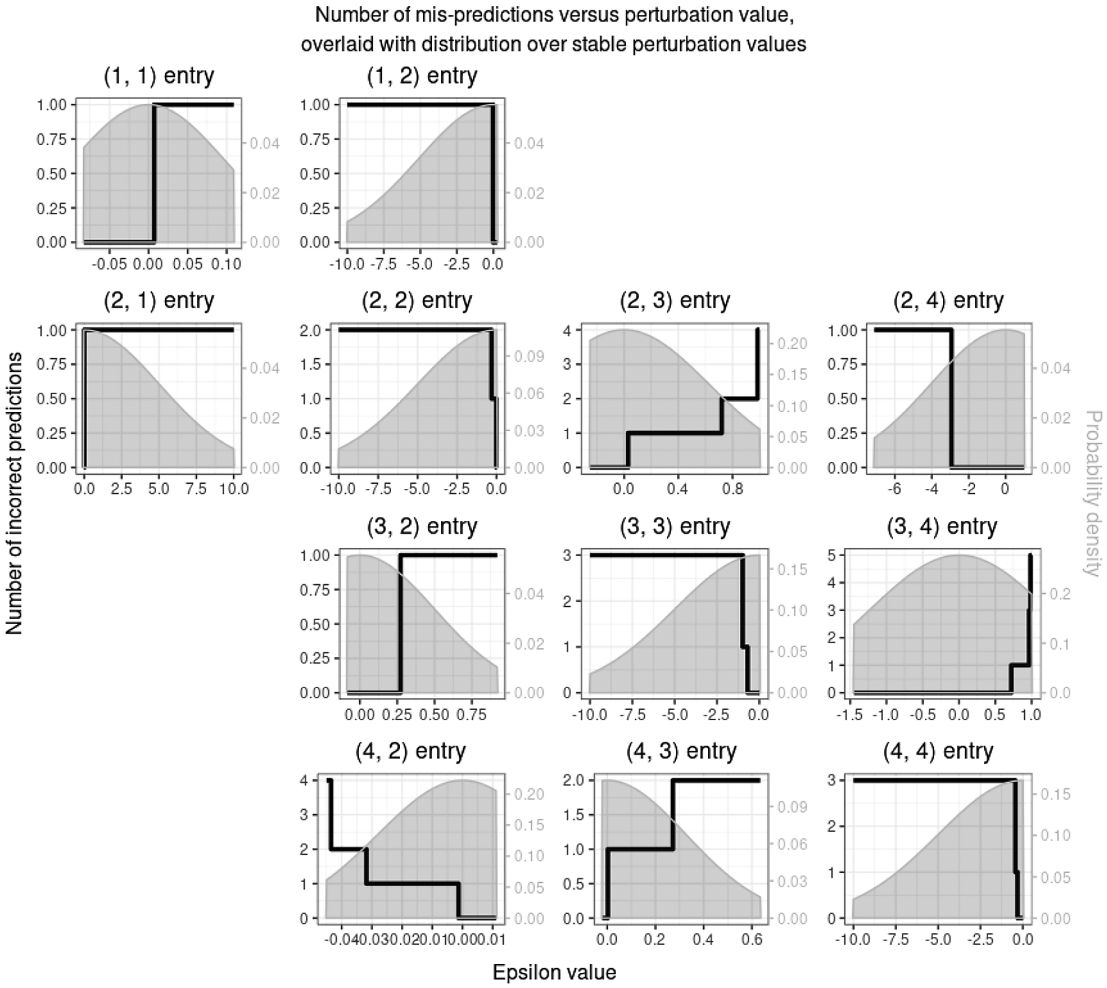

Figure 2. **Visualization produced by the R package function `GenerateEntryWiseFigures` depicting the assumed uncertainty distribution associated with each non-zero Jacobian element in a four-species intra-guild predation network (grey distributions) and the consequent number of qualitative mispredictions (sign switches) that a given magnitude of uncertainty in each element will incur in the net effects matrix of the network as a whole (black lines).**

parameterizations to be specified for each interaction strength uncertainty in both the single and multiple edge computations. Lastly, other theorems contained in Ref. 11, including those relating to the characterization of quantitative mispredictions, may also be implemented.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

`PressPurt` is available from: `https://cran.r-project.org/web/packages/PressPurt/`

Source code available from: `https://github.com/dkoslicki/PressPurt`

Archived source code as at time of publication: `https://doi.org/10.5281/zenodo.5661173`[29]

License: MIT

References

1. Antoniewicz MR: **Methods and advances in metabolic flux analysis: a mini-review.** *J. Ind. Microbiol. Biotechnol.* 2015; **42**(3): 317–325.
PubMed Abstract | Publisher Full Text
2. Bender EA, Case TJ, Gilpin ME: **Perturbation experiments in community ecology: theory and practice.** *Ecology.* 1984; **65**(1): 1–13.
Publisher Full Text
3. Chassagnole C, Noisommit-Rizzi N, Schmid JW, *et al.*: **Dynamic modeling of the central carbon metabolism of Escherichia coli.** *Biotechnol. Bioeng.* 2002; **79**(1): 53–73.
PubMed Abstract | Publisher Full Text
4. Csardi G, Nepusz T: **The igraph software package for complex network research.** *InterJournal, Complex Systems: 1695.* 2006.
5. Dahlquist KD, Fitzpatrick BG, Camacho ET, *et al.*: **Parameter estimation for gene regulatory networks from microarray data: Cold shock response in *Saccharomyces cerevisiae.*** *Bull. Math. Biol.* 2015; **77**(8): 1457–1492.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Dambacher JM, Li HW, Rossignol PA: **Relevance of community structure in assessing indeterminacy of ecological predictions.** *Ecology.* 2002; **83**(5): 1372–1385.
Publisher Full Text
7. Deyle ER, May Robert M, Munch Stephan B, *et al.*: **Tracking and forecasting ecosystem interactions in real time.** *Proc. R. Soc. B Biol. Sci.* 2016; **283**(1822) 20152258, 2019/06/12: 20152258.
Publisher Full Text
8. Dinno A: **Loopanalyst: A collection of tools to conduct levins' loop analysis.** 2018.
Reference Source
9. Gauzens B, Barnes A, Giling DP, *et al.*: **fluxweb: An r package to easily estimate energy fluxes in food webs.** *Methods Ecol. Evol.* 2019/06/12 2019; **10**(2): 270–279.
Publisher Full Text
10. Khatibipour MJ, Kurtoğlu F, Çakir T: **Jacly: a jacobian-based method for the inference of metabolic interactions from the covariance of steady-state metabolome data.** *PeerJ.* 12 2018; **6**: e6034–e6034.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Koslicki D, Novak M: **Exact probabilities for the indeterminacy of complex networks as perceived through press perturbations.** *J. Math. Biol.* 2018; **76**(4): 877–909.
PubMed Abstract | Publisher Full Text
12. Levins R: *Evolution in Changing Environments: Some Theoretical Explorations. Monographs in Population biology.* Princeton, N.J.: Princeton University Press; 1968.
Publisher Full Text
13. Levins R: **The qualitative analysis of partially specified systems.** *Ann. N. Y. Acad. Sci.* 1974; **231**: 123–138.
PubMed Abstract | Publisher Full Text
14. Melbourne-Thomas J, Wotherspoon S, Raymond B, *et al.*: **Comprehensive evaluation of model uncertainty in qualitative network analyses.** *Ecol. Monogr.* 2012; **82**(4): 505–519.
Publisher Full Text
15. Mueller LAJ, Kugler KG, Dander A, *et al.*: **QuACN: an R package for analyzing complex biological networks quantitatively.** *Bioinformatics.* 11 2010; **27**(1): 140–141.
PubMed Abstract | Publisher Full Text
16. Mark Novak J, Wootton T, Doak DF, *et al.*: **Predicting community responses to perturbations in the face of imperfect knowledge and network complexity.** *Ecology.* 2011; **92**(4): 836–846.
PubMed Abstract | Publisher Full Text
17. Novak M, Yeakel J, Noble AE, *et al.*: **Characterizing species interactions to understand press perturbations: What is the community matrix?.** *Annu. Rev. Ecol. Evol. Syst.* 2016; **47**: 409–432.
Publisher Full Text
18. Pomeranz JPF, Thompson RM, Poisot T, *et al.*: **Inferring predator–prey interactions in food webs.** *Methods Ecol. Evol.* 2019/06/12 2019; **10**(3): 356–367.
Publisher Full Text
19. Rajala M, Ritala R: **Topology estimation method for telecommunication networks.** *Telecommun. Syst.* 2018; **68**(4): 745–759.
Publisher Full Text
20. Rand DA: **Mapping global sensitivity of cellular network dynamics: sensitivity heat maps and a global summation law.** *J. R. Soc. Interface.* 2019/06/12 2008; **5**(suppl_1): S59–S69.
21. Rice JJ, Yuhai T, Stolovitzky G: **Reconstructing biological networks using conditional correlation analysis.** *Bioinformatics.* 6/12/2019 2004; **21**(6): 765–773.
Publisher Full Text
22. Schlauch D, Paulson JN, Young A, *et al.*: **Estimating gene regulatory networks with pandaR.** *Bioinformatics.* 03 2017; **33**(14): 2232–2234.
PubMed Abstract | Publisher Full Text | Free Full Text
23. Sontag E, Kiyatkin A, Kholodenko BN: **Inferring dynamic architecture of cellular networks using time series of gene expression, protein and metabolite data.** *Bioinformatics.* 2004; **20**(12): 1877–1886.
PubMed Abstract | Publisher Full Text
24. Rachel Wang YX, Huang H: **Review on statistical methods for gene network reconstruction using expression data.** *J. Theor. Biol.* 2014; **362**(0): 53–61.
Publisher Full Text
25. Willing BP, Russell SL, Finlay BB: **Shifting the balance: antibiotic effects on host–microbiota mutualism.** *Nat. Rev. Microbiol.* 02 2011; **9**: 233–243.
Publisher Full Text
26. Yodzis P: **The indeterminacy of ecological interactions as perceived through perturbation experiments.** *Ecology.* 1988; **69**(2): 508–515.
Publisher Full Text
27. Yodzis P: **Must top predators be culled for the sake of fisheries?.** *Trends Ecol. Evol.* 2001; **16**(2): 78–84.
PubMed Abstract | Publisher Full Text
28. Zamir E, Bastiaens PIH: **Reverse engineering intracellular biochemical networks.** *Nat. Chem. Biol.* 2008; **4**(11): 643–647.
PubMed Abstract | Publisher Full Text
29. Koslicki D, Novak M: **dkoslicki/PressPurt: v1.0.1 (v1.0.1).** *Zenodo.* 2021.
Publisher Full Text