



SOFTWARE TOOL ARTICLE

PressPurt: network sensitivity to press perturbations under interaction uncertainty

[version 1; peer review: awaiting peer review]

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V1 First published: 11 Feb 2022, 11:173

<https://doi.org/10.12688/f1000research.52317.1>

Latest published: 11 Feb 2022, 11:173

<https://doi.org/10.12688/f1000research.52317.1>

Open Peer Review

Approval Status 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



This article is included in the RPackage gateway.



This article is included in the Python collection.

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Author roles: **Koslicki D:** Conceptualization, Funding Acquisition, Investigation, Methodology, Software, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Gibbon D:** Software, Writing – Review & Editing; **Novak M:** Conceptualization, Investigation, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This material is based upon work supported by the National Science Foundation under Grant No. 1664803 (PI David Koslicki).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Koslicki D, Gibbon D and Novak M. **PressPurt: network sensitivity to press perturbations under interaction uncertainty [version 1; peer review: awaiting peer review]** F1000Research 2022, 11:173
<https://doi.org/10.12688/f1000research.52317.1>

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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 $\frac{dN_i}{dt} = f_i(\vec{N}) + u_i$ for $i = 1, \dots, n$ variables. Here, $f_i(\vec{N})$ 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 Matrix¹²: the Jacobian of the system evaluated at a stable equilibrium point, $A_{i,j} = \left. \frac{\partial f_i(\vec{N})}{\partial N_j} \right|_{x^*}$. `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, $\frac{\partial N_i}{\partial u_j} = -A_{i,j}^{-1}$.^{6,17,20} 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.

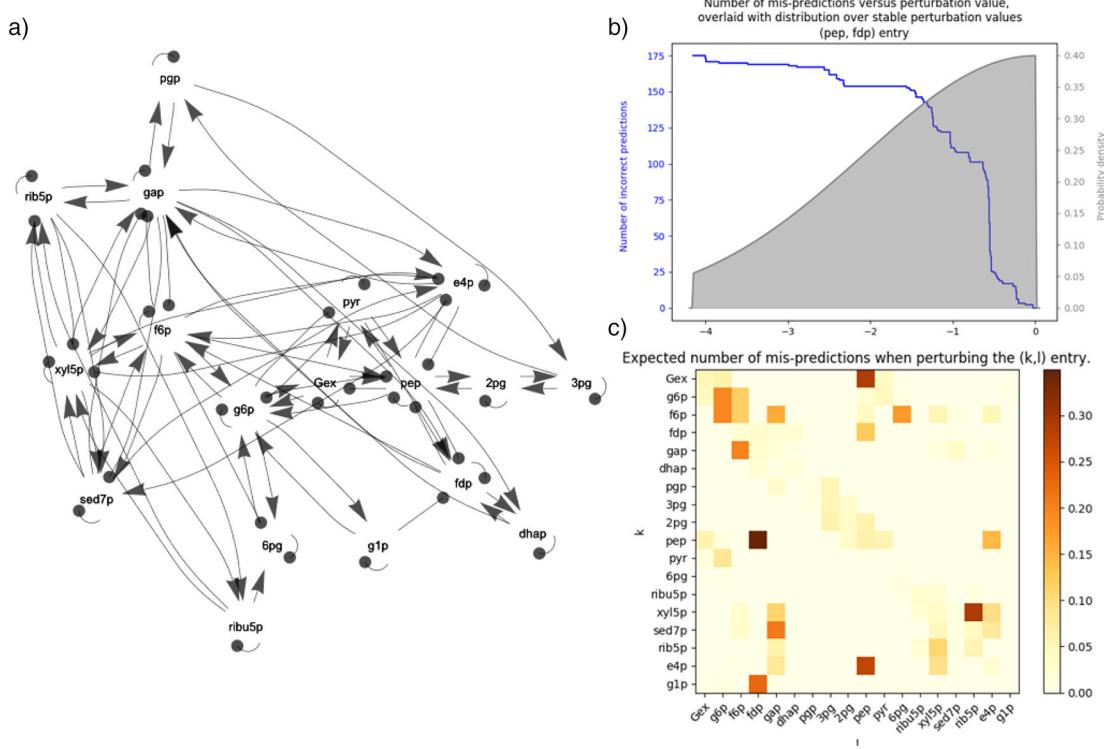


Figure 1. We demonstrate the PressPurt package on the *Escherichia coli* metabolic network inferred by Ref. 3 and quantified in Jacobian form by Ref. 10. Panel a) shows the network with positive and negative interactions depicted with arrowheads and balls respectively. Panel b) shows how uncertainty 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 matrix¹¹

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

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 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

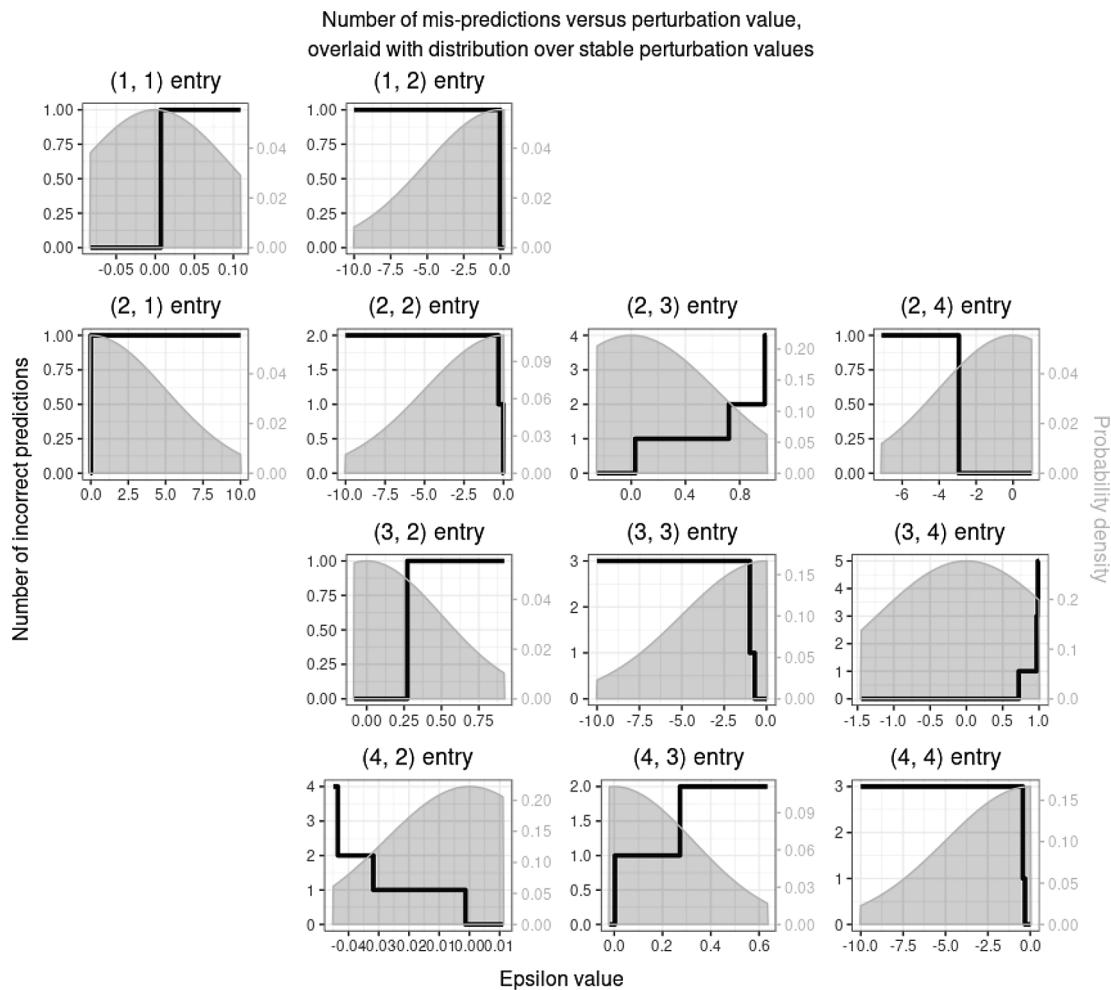


Figure 2. Visualization produced by the R package function `GenerateEntryWiseFigures` depicting the assumed uncertainty distribution associated with each non-zero Jacobian element in a four-species intra-guild predation network (grey distributions) and the consequent number of qualitative mispredictions (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

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