Using a smoother approach IMPRES-M to identify and characterize multi-layered turnover networks

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Objectives & Introduction

Objectives: Identify and characterize multi-layered turnover networks of biomarkers with IMPRES-M.

Introduction: Turnover systems can carry the dynamic response of biomarkers to a drug.

- The production and elimination of the some molecules are directly stimulated or inhibited by a drug, whereas these molecules might subsequently influence the activities of downstream molecules, resulting in a layered network of biomarker turnover.
- We aim to identify the responsive relationships between biomarkers and reconstruct the multi-layered turnover networks based on the concentration profiles of the biomarkers.
- We characterized biomakers in the reconstructed turnover netwrok with IMPRES-M and evaluated the robustness of the approach with noise on the concentration profiles.

Conclusions & Discussion

- The structure of the multi-layered turnover network was accurately identified by evaluating the pairwise biomarker turnover relationships in the system with IMPRES-M and integrating estimated parameters.
- We characterized the layered networks by efficiently estimating the parameters of the turnover markers with IMPRES-M and alleviating the necessity of parameter estimations of ordinary differential equation (ODE) systems.
- In the future, the turnover system could be extended to manage the effects on the removal of molecules and a more complex relation function of molecule effects f.
- The impact of noise on the reconstruction of the multi-layered turnover network needs to be further evaluated.

Methods & Results

Settings of the PK-PD turnover system

- A four-layered network was created as shown in Figure 1A:
  - The first layer contains biomarkers directly affected by the drug concentration profiles in plasma;
  - Three additional layers of downstream biomarkers;
  - Each downstream biomarker was affected by one corresponding biomarker in the previous layer;
  - Each layer includes 5 inhibited and 5 stimulated biomarkers.
- For the simulation of the system (Figure 1B), the production of a component representing a biomarker is stimulated or inhibited by one upstream molecule (i.e. the drug or another biomarker), through the relationship

$$\frac{dE}{dt} = k_{in} \cdot f(C) - k_{out} \cdot E \tag{1}$$

where the E and C are the target biomarker and the upstream molecule concentration over time t. k_{in} and k_{out} are parameters controlling molecule productions and eliminations. $f(C)$ characterizes a "linear" effect as $1 - \alpha \cdot C(t)$.

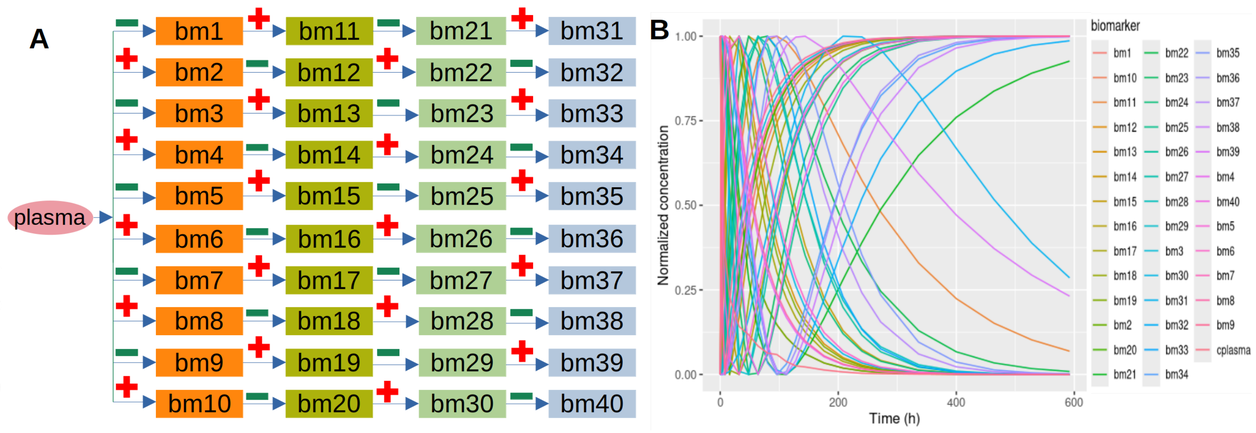

Fig. 1: Representation of the multi-layered turnover network.

Network structure reconstruction

In this section, we aim to reconstruct the turnover system in Figure 1A based on the concentration profiles of the plasma and biomarkers simluated in Figure 1B.

- The PK-PD relationship between the plasma and each biomarker were evaluated with the goodness of fitting (i.e. R-squared) using IMPRES-M*. A better fitting indicates that the biomarker is more directly influenced by the plasma (i.e. with fewer intermediate biomarker(s) between them) (Figure 2A).
- A network of biomarkers was constructed as Figure 2B:
  - All biomarkers are nodes and all pair combinations of biomakers are edges;
  - The edges are directed, from the biomarker closer the plasma (driver biomarker) to the target biomarker;
  - For each pair combination, the parameters k_{in}, k_{out} , and α are evaluated with IMPRES-M*.
- Three affinity matrices were constructed for the parameters k_{in}, k_{out} , and α, respectively, with each cell filled with the estimated value of the pair combinations of biomarkers (Figure 2C).
- The three affinity matrices were fused into one matrix with the algorithm Similarity Network Fusion (SNF), integrating the important information carried by each parameter (Figure 2D).
- K-means clustering was performed on the fused matrices, stratifying biomarkers into different layers in the turnover network.
- For each target biomarker, their driver biomarker was identified by selecting the best R-squared of all pair combinations with biomarkers from the previous layers.

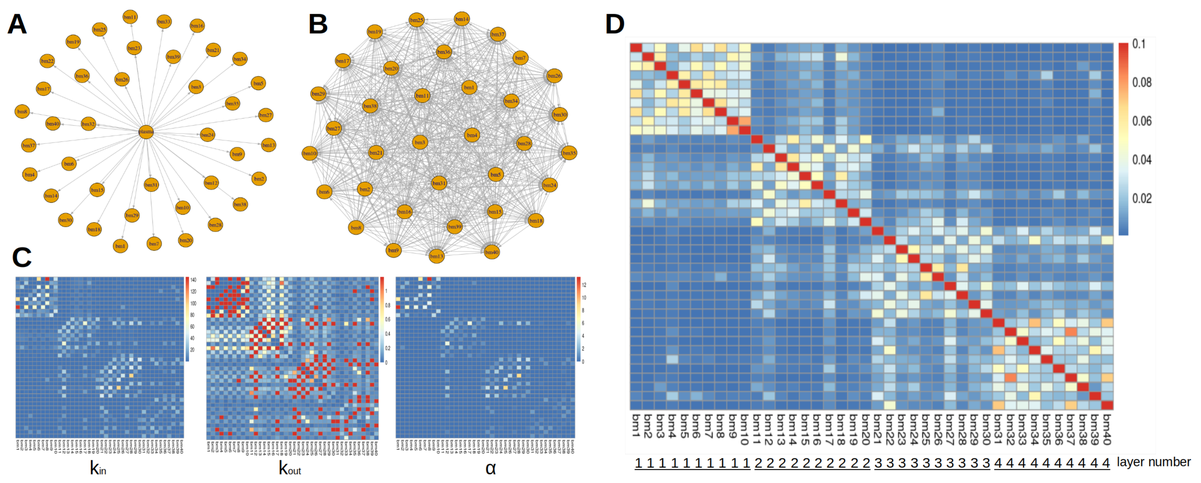

Fig. 2: Representation of four clusters representing the four layers on fused matrices.

*Turnover relationship evaluation with IMPRES-M [1, 2]:

- The plasma/driver biomarker concentration $C(t)$ is represented as a linear combination of B-spline functions;
- The rectangle rule integration is applied to approximate the target biomarker concentration $E(t)$ while evaluating the parameters

Characterization of the network

After identifying the structure of the four-layered network, IMPRES-M was utilized to characterize the biomarkers in the network and its accuracy was evaluated as a function of increasing complexity.

- Parameters k_{in}, k_{out} , and α were estimated for each biomarker in turnover models.
- Proportional error was added to the concentration profiles to evaluate the robustness of IMPRES-M evaluation with noise.
- The mean fold change (MFC, in %) was calculated as

$$\text{Mean Fold Change} = \frac{1}{n}\sum_{i=1}^{n}\frac{|Observed_i - Predicted_i|}{Observed_i} \times 100\%$$

The overall run time for this system of 40 markers was under 1 minute, and the results in Table 1 showed that:

- IMPRES-M effectively estimated the biomarker parameters in the four-layer turnover network.
- The estimation of k_{in} and k_{out} appear to be more accurate than that of α.
- Increased residual errors resulted in higher MFC values of estimated parameters.
- The depth of a layer does not appear to have an impact on the accuracy of the estimations.

Table 1: The mean fold change (in %) between estimated and actual parameters of the biomarkers.

Error Rate	kin overall	kin per layer 1-4	kout overall	kout per layer 1-4	alpha overall	alpha per layer 1-4
No Error	0.56	2.1 0.12 0.01 0.02	0.60	2.2 0.13 0.01 0.02	57	66 58 51 55
Proportional error 0.01	8.1	3.8 9.2 10 9.3	9.1	4.1 11 11 10	63	66 59 63 62
Proportional error 0.02	23	15 22 22 26	18	10 11 16 29	66	59 71 68 65
Proportional error 0.05	40	13 76 28 50	47	13 76 52 54	87	74 148 70 68

References

[1] Elassaiss-Schaap, J., Cifelli, L., and Eilers P.H. *Construction of IMPRES-M, a non-parametric impulse-response modeling method, in the context of varying pharmacokinetic profiles.* In *PAGE Conference*, June, 2024.

[2] Mohammed Ali, Z., Cifelli, L., Elassaiss-Schaap, J. *Evaluation of extrapolation potential of IMPRES-M, a non-parametric Impulse-Response Modeling framework when applied to pharmacokinetic profiles of different dosing frequencies.* In *PAGE Conference*, June, 2024.

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