Identification of Unintuitive Features of Sumoylation through Mathematical Modeling

Shraddha S. Puntambekar, Dimpal Nyayanit, Priyanka Saxena, and Chetan J. Gadgil

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About SUMO and The Complexities of Sumoylation

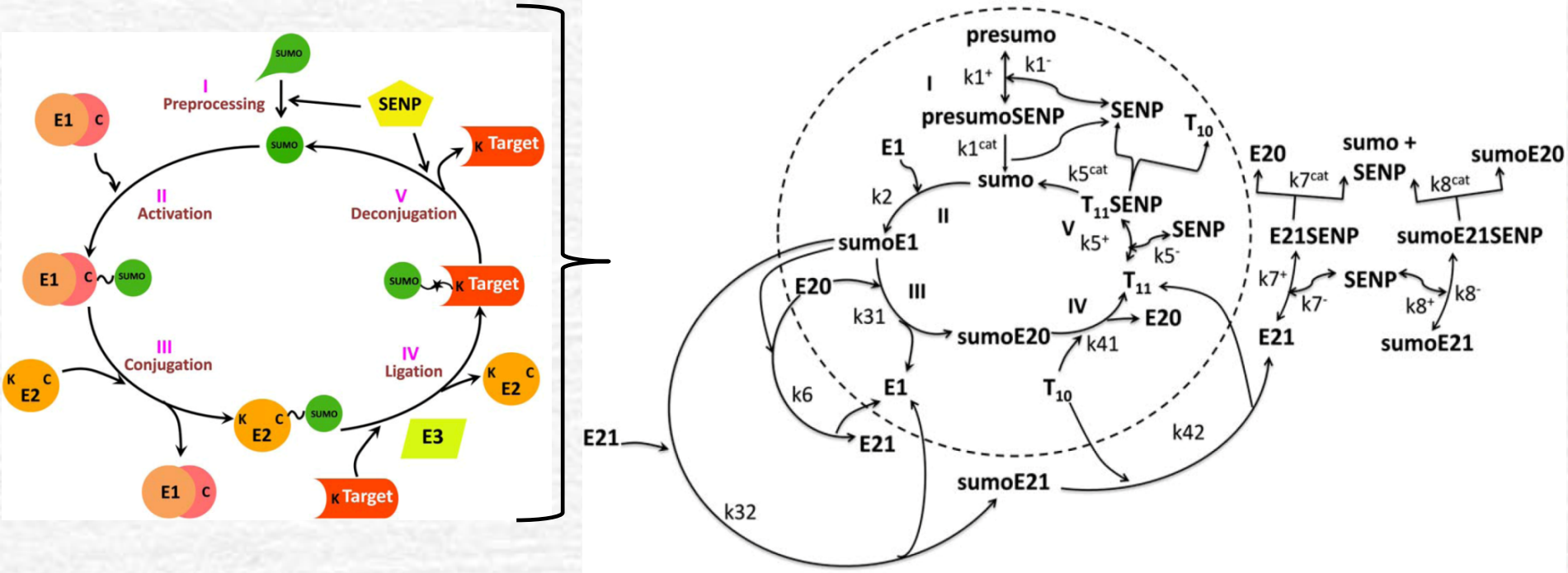
Sumoylation is a **post translational modification** in which a **Small Ubiquitin like Modifier (SUMO)** protein is reversibly covalently attached to lysine of the target protein

➢Is a multistep, multi-enzyme, reversible process
➢Is involved in regulation of several cellular processes like replication, transcription and nuclear transport
➢SUMO modification of the target can lead to a conformational change in the target, can its binding affinity/specificity and specific activity

- ➢ Sumoylation of multiple targets each to a different extent.
- ➢ Autosumoylation of E2 and consequent change in the activity
- ➢ Long term response captured by simulating an open system, while shorter time scale response studied by simulating a closed system.
- ➢ One of the system's enzyme - SENP functions in both sumoylation and desumoylation of the target

For further information contact cj.gadgil@ncl.res.in

The first mathematical model for the SUMO system



Steps involved in sumoylation of a target protein (T_{10}) and the system's enzyme E2 (E20) are represented as chemical reactions and rate kinetics are modeled using standard chemical reaction engineering techniques.

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Analysis reveals 3 unintuitive results

1) The short term (open system) behaviour differs qualitatively from the long-term (closed system) dynamics

2) Long-term steady state levels of the sumoylated target are robust to variation in the parameters of the conjugation ligation steps and to the properties of E2.
   Sometimes, enzyme properties do not matter

3) Even for the cases when autosumoylation of modifying enzyme E2 results in its equal or higher activity, the long-term steady state sumoylated target levels are lower than in a system with no E2 modification.
   More efficient catalyst need not result in more product

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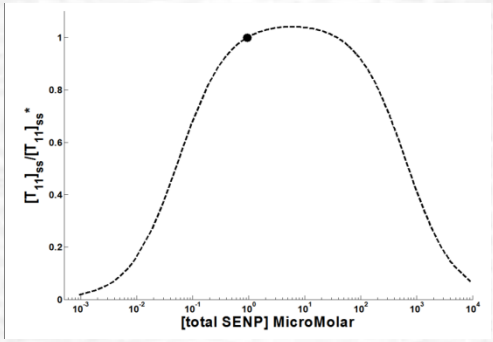
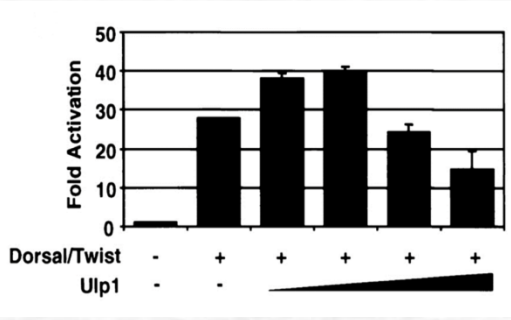
Using the model to generate testable hypothesis

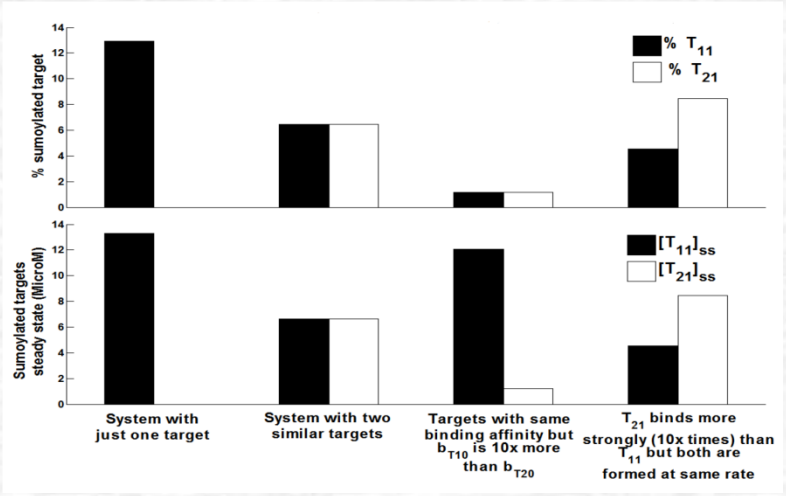
The model prediction of an optimal SENP level for an open system is in accordance with a study of Smt3 conjugation to Dorsal protein in Drosophila S2 cells





Bhaskar, Vinay, Matthew Smith, and Albert J. Courey. "**Conjugation of Smt3 to dorsal may potentiate the Drosophila immune response**." Molecular and cellular biology 22.2 (2002): 492-504.

Model predicts low sumoylation levels, consistent with experimental observations; and suggests that limitation in availability of SUMO is the reason for lower sumoylation



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