Computational Systems Biology of Cancer Metastasis

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Cancer Systems Biology Lab

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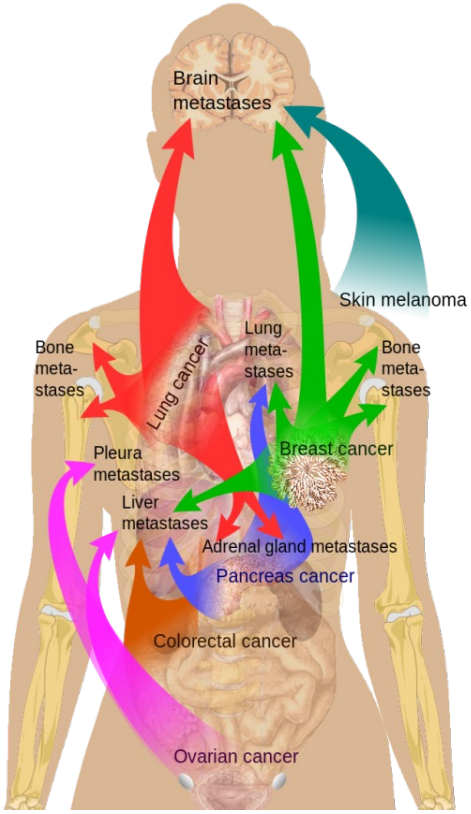
Cancer metastasis: an unsolved clinical challenge



- Metastasis causes more than 90% of all cancer-related deaths and is clinically insuperable.
- Metastasis is an extremely challenging process for cells, with > 98% attrition rates.
- Cancer cells that successfully metastasize **dynamically change many traits together**:

✓ Ability to adhere, migrate and invade

✓ Evading attacks by immune system + drugs given

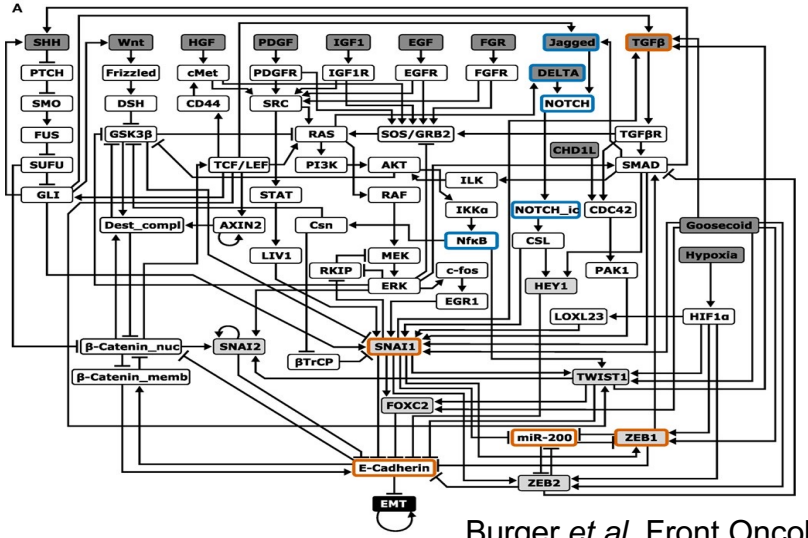
✓ Settling down in a new organ and colonizing it

To develop a therapy against metastasis, we first need a dynamic and systems-level understanding of the process to identify how cells alter these multiple traits together.

A systems-level understanding means…

1. Realizing that integrating different parts can lead to novel behaviors/functions, i.e. whole is greater than sum of its parts

2. Being able to predict the behavior of the system in varied conditions



Burger *et al.* Front Oncol 2017

We can mathematically model these biological networks to achieve a systems-level understanding, similar to that attained for engineered systems as shown above

A generalized systems biology workflow

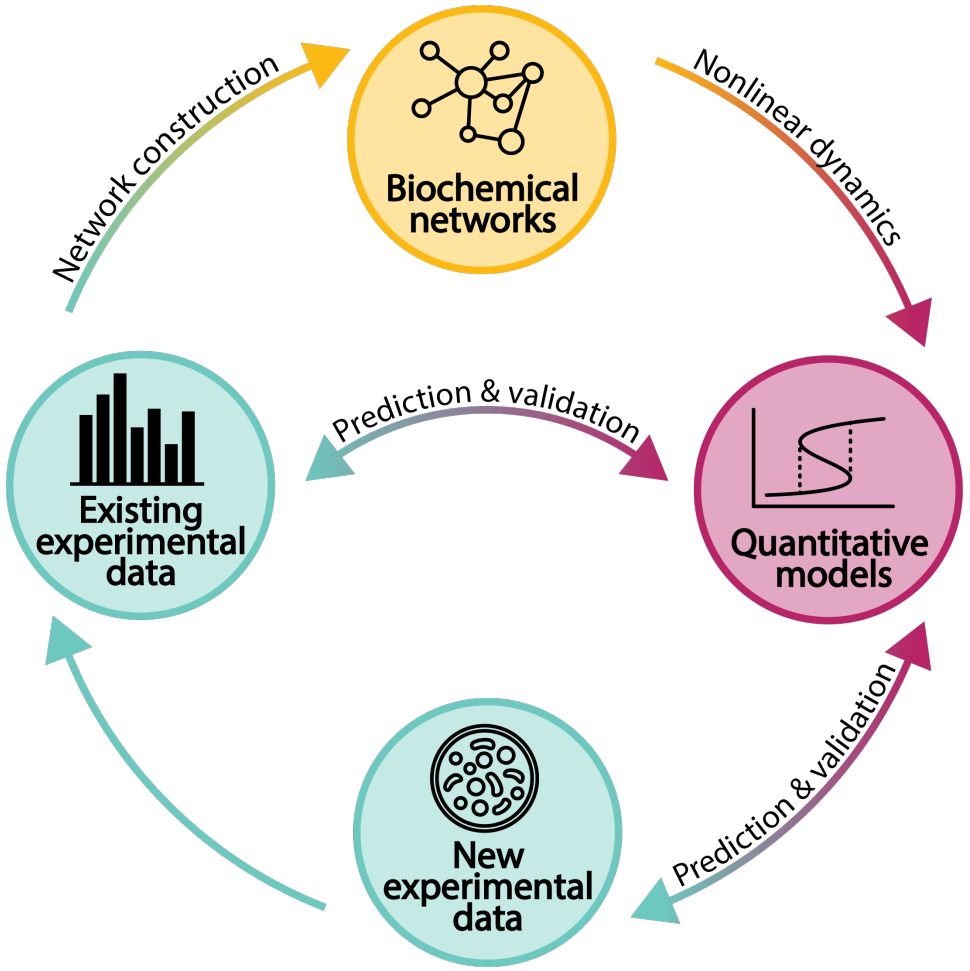
Steps involved in ITeRaTe workflow:

1. Identify core players based on published experimental data (gene expression profiles, qPCR/Western Blot data, RNA-seq/ChIP-seq data, overexpression experiments etc.)

2. Construct regulatory network formed by interconnections among those players

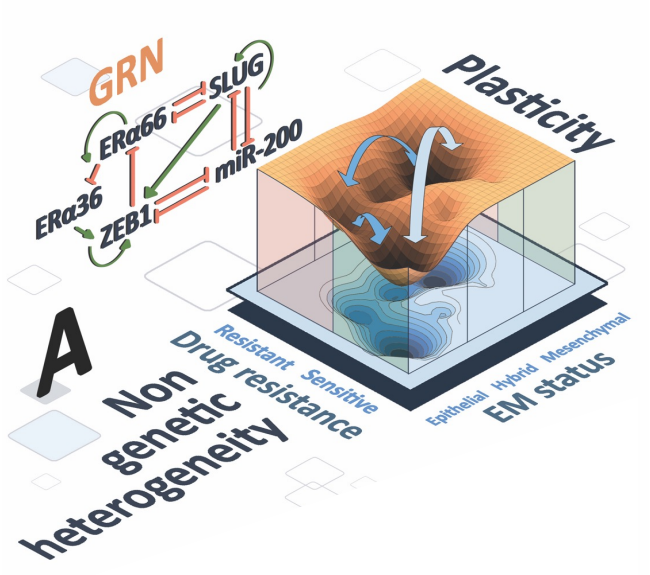
1. Simulate the dynamics of regulatory network; compare with experiments, propose new experiments to do

Input, Test, Refine, and Test (ITeRaTe)



Jolly *et al.* Pharmacology & Therapeutics 2018

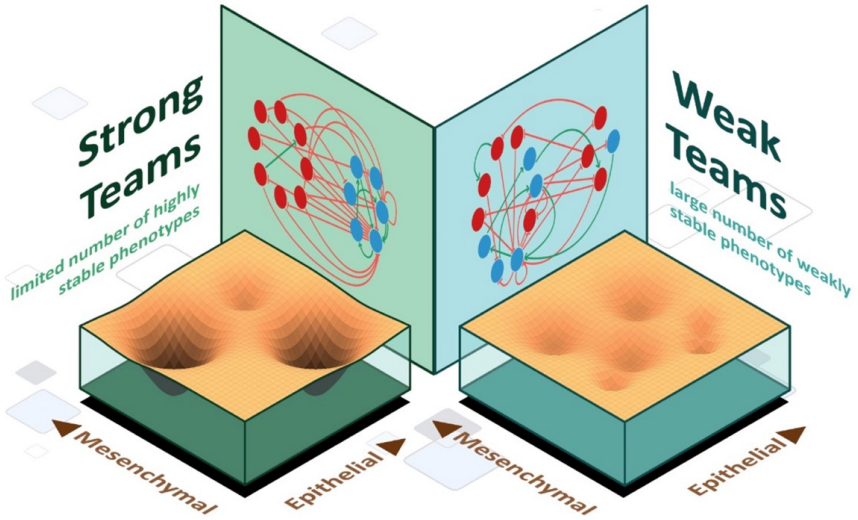
Previous work done by our group



Interconnected feedback loops can enable:

a) Epithelial-mesenchymal transition (EMT) drives resistance to tamoxifen (breast cancer drug)
AND
b) Resistance to tamoxifen drives EMT

Sahoo *et al.* NAR Cancer 2021 (PMID: 34316714)



Presence of “teams” supporting epithelial and mesenchymal phenotypes can allow higher plasticity and stemness of the hybrid epithelial/mesenchymal phenotypes.

Hari *et al.* eLife 2022 (PMID: 36269057)

Tools and techniques used

- Mathematical modeling of biological regulatory networks
- Simulating a set of ordinary (and/or partial) differential equations
- Analyzing experimental transcriptomics/proteomics, and clinical data

Required background

- Basic understanding of ordinary differential equations and nonlinear dynamics (or the self-driven will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in both cancer biology and systems biology)
- **Note:** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology

Further reading

- Kolch, W.; Halasz, M.; Granovskaya, M.; Kholodenko, B. N. The dynamic control of signal transduction networks in cancer cells. Nat. Rev. Cancer 2015, 15 (9), 515–27. doi: 10.1038/nrc3983
- Magi, S.; Iwamoto, K.; Okada-Hatakeyama, M. Current status of mathematical modeling of cancer – From the viewpoint of cancer hallmarks. Curr. Opin. Syst. Biol. 2017, 2, 38-47. doi: 10.1016/j.coisb.2017.02.008