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Computational modeling of EGFR signaling with hybrid coarse- and fine-grained modules

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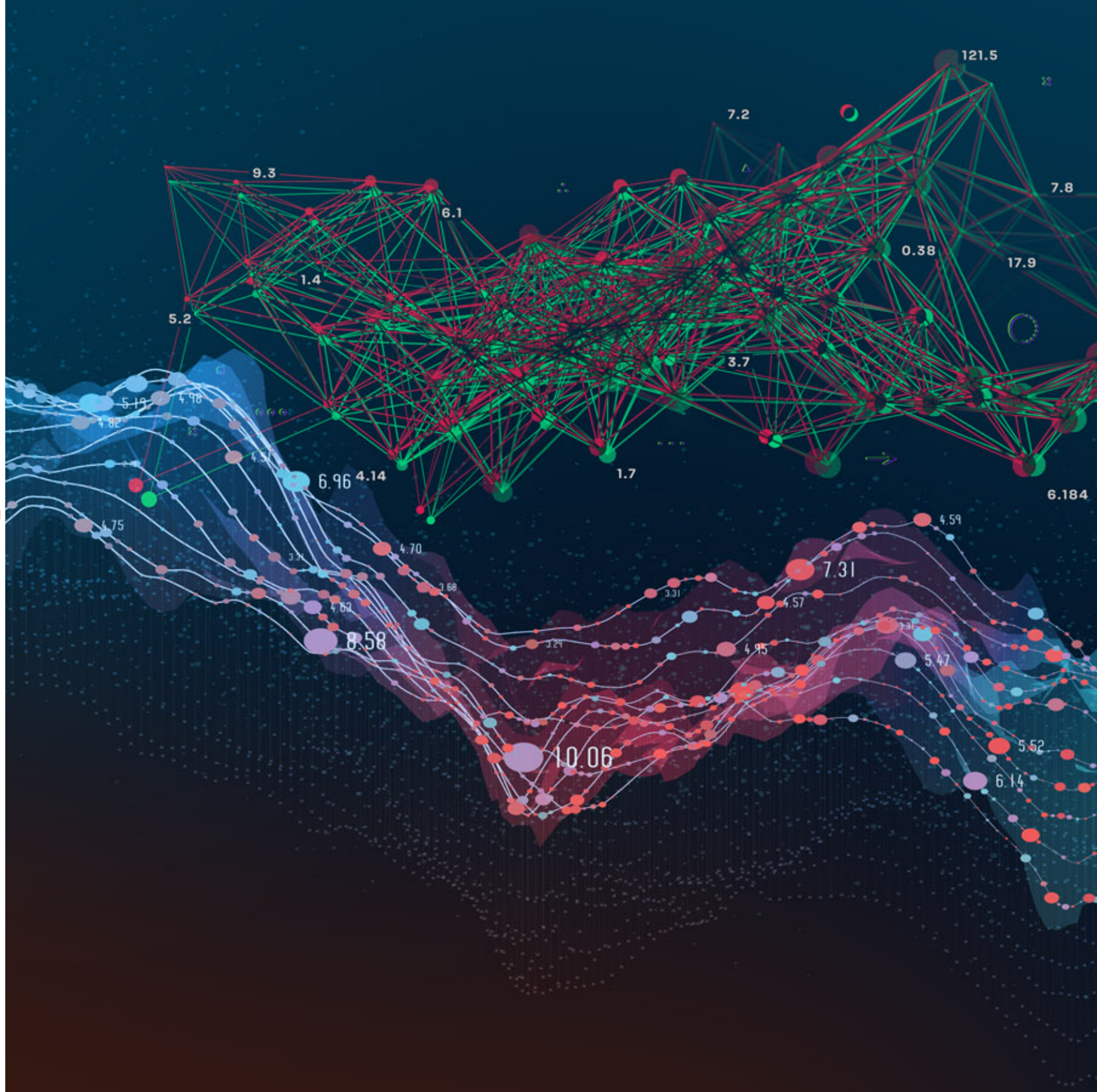

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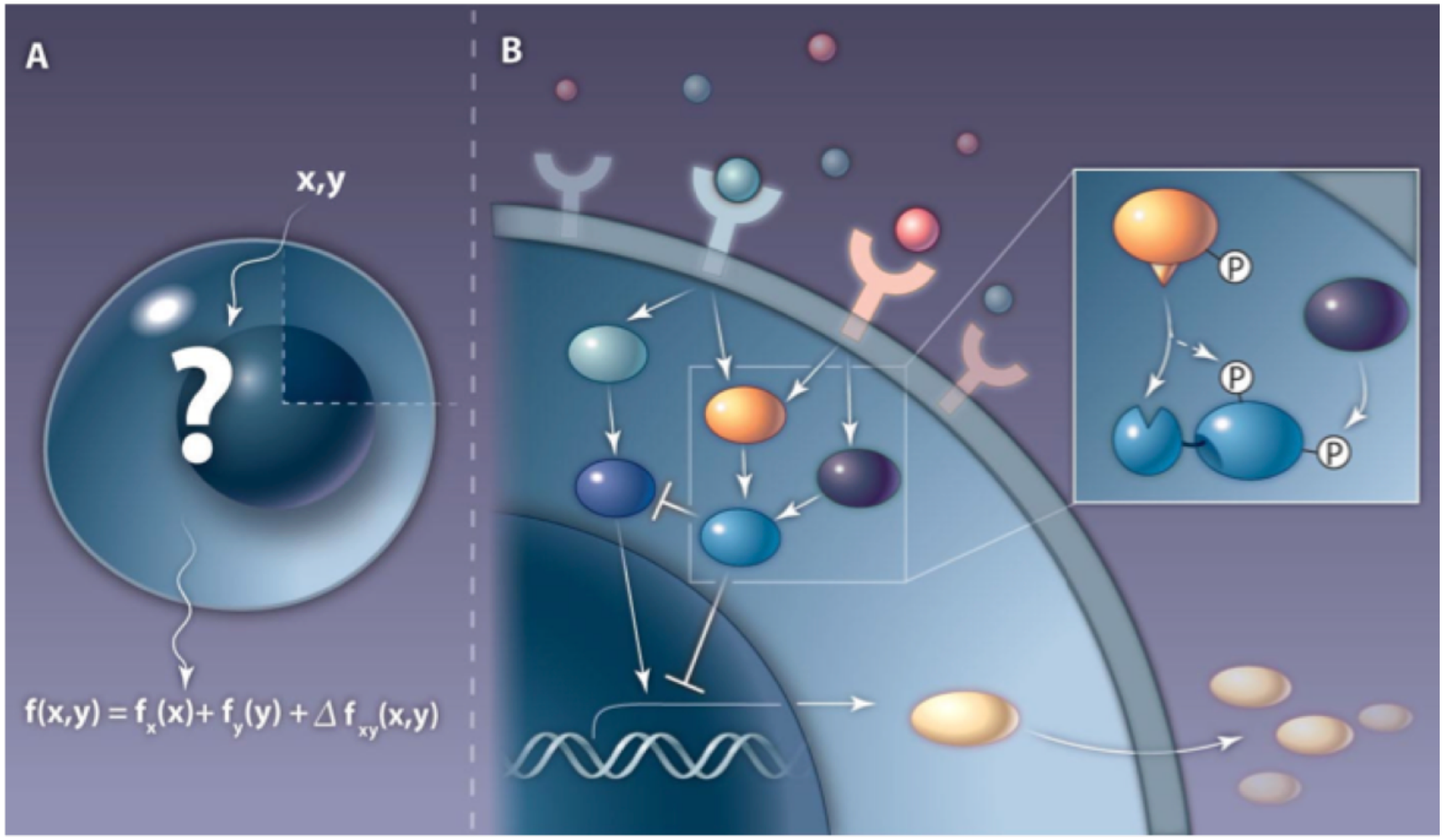
Cellular information processing



W. S. Hlavacek, J. R. Faeder, *Sci. Signal.* 2, pe46 (2009)

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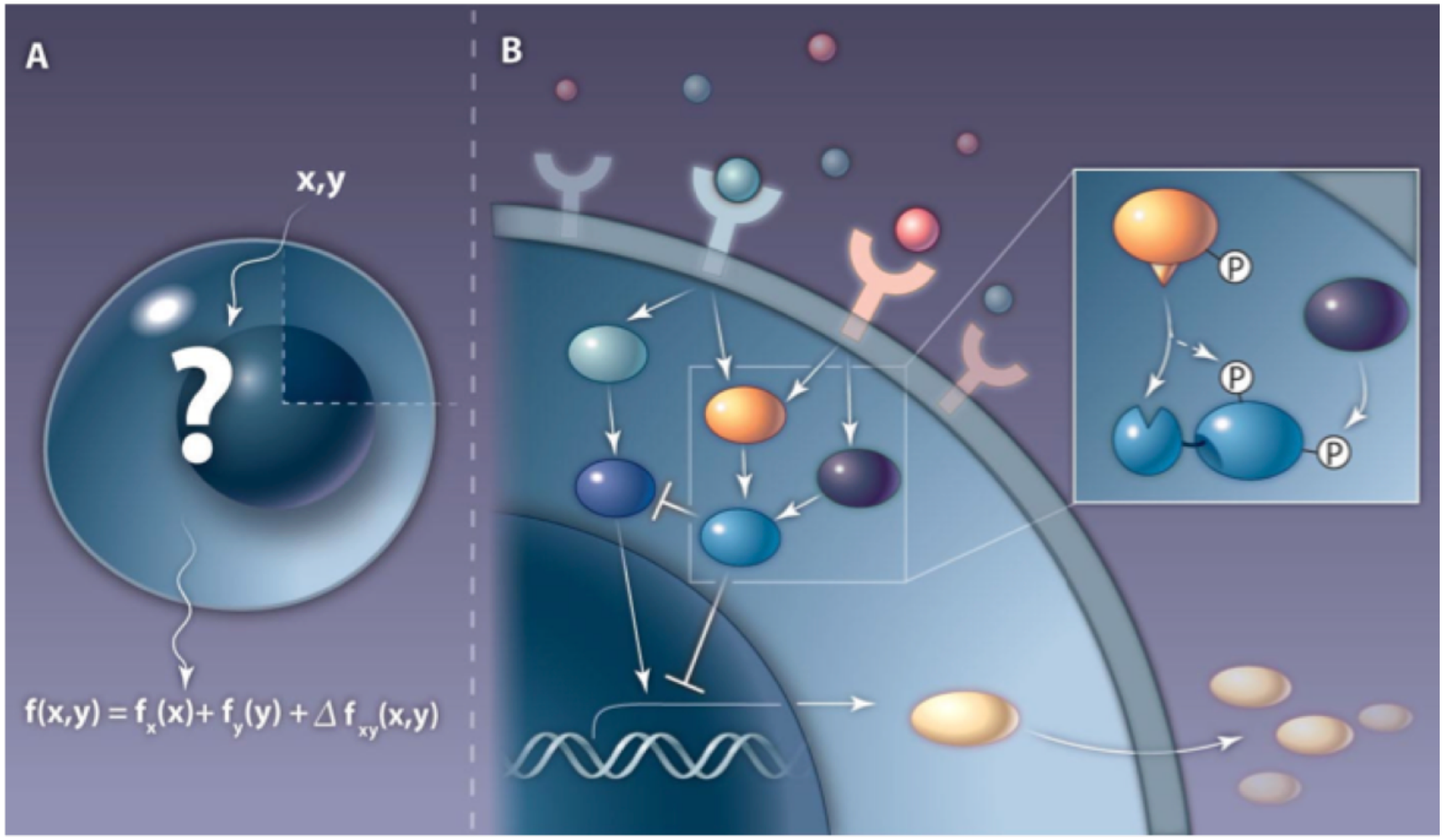

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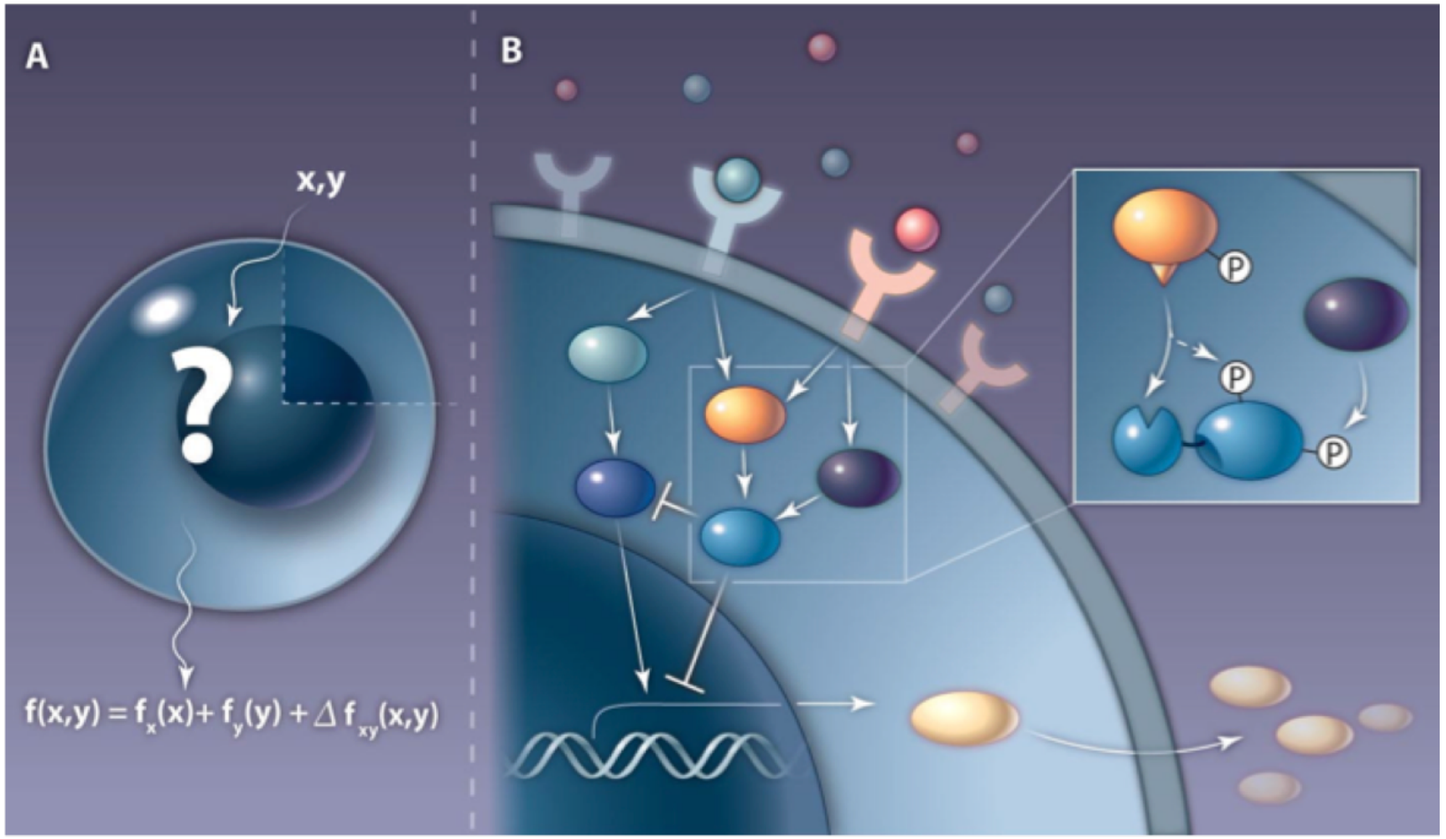
Environmental signals

$$\frac{dx_i}{dt} = \sum_{j=1}^{m} \nu_{j,prod} - \sum_{k=1}^{m} \nu_{k,cons}$$

where $\nu_j = f(x_1, x_2, \cdots, x_n, S_1, S_2, \cdots, S_l)$, $x_i(0) = x_{i,0}$

Cellular decision-makings

Cellular information processing



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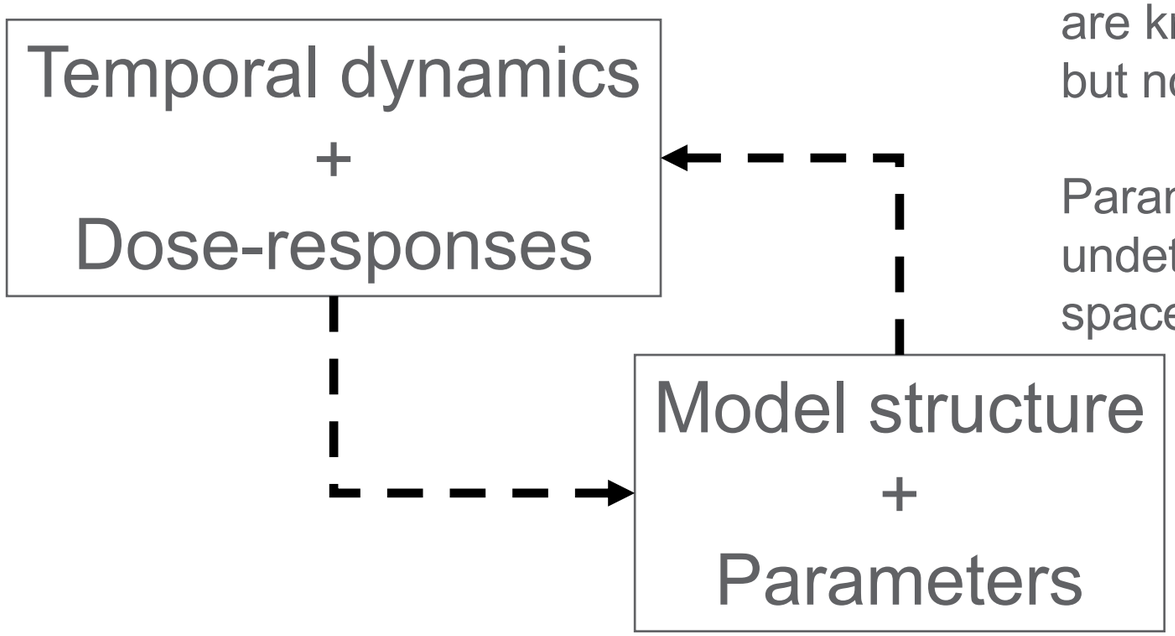
Cellular decision-makings

Temporal dynamics
+
Dose-responses

Model structure
+
Parameters

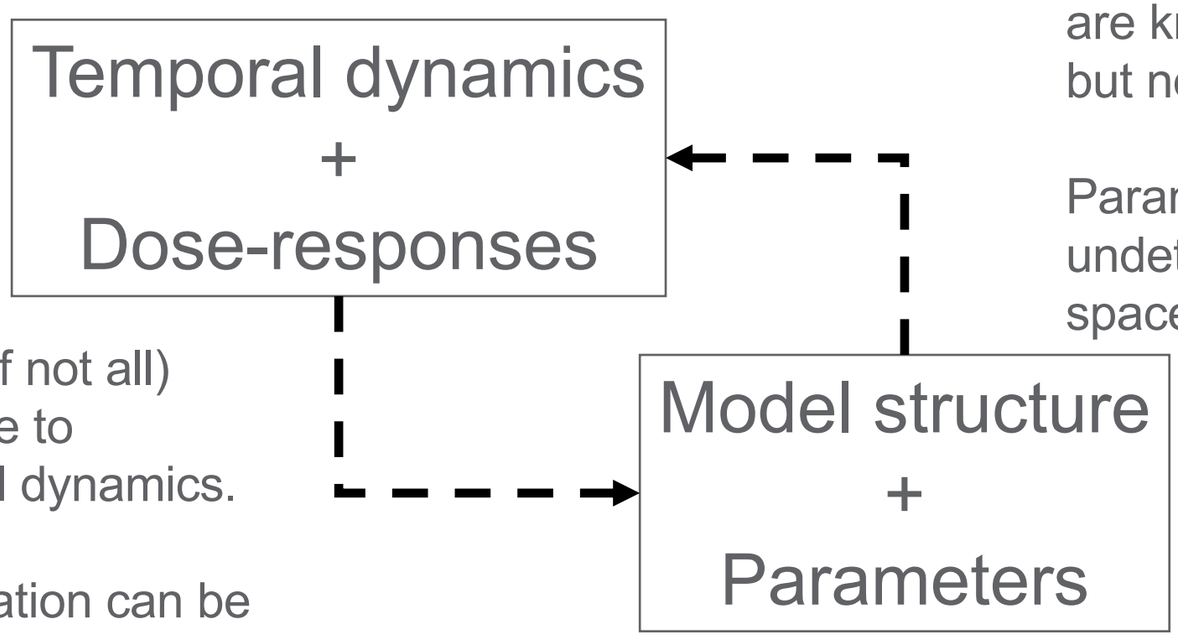
Sparsity of measurements and knowledge



Not all molecular interactions are known. Some are known but not in details.

Parameters are mostly undetermined, thus parameter space is large

Sparsity of measurements and knowledge



Not all molecular interactions are known. Some are known but not in details.

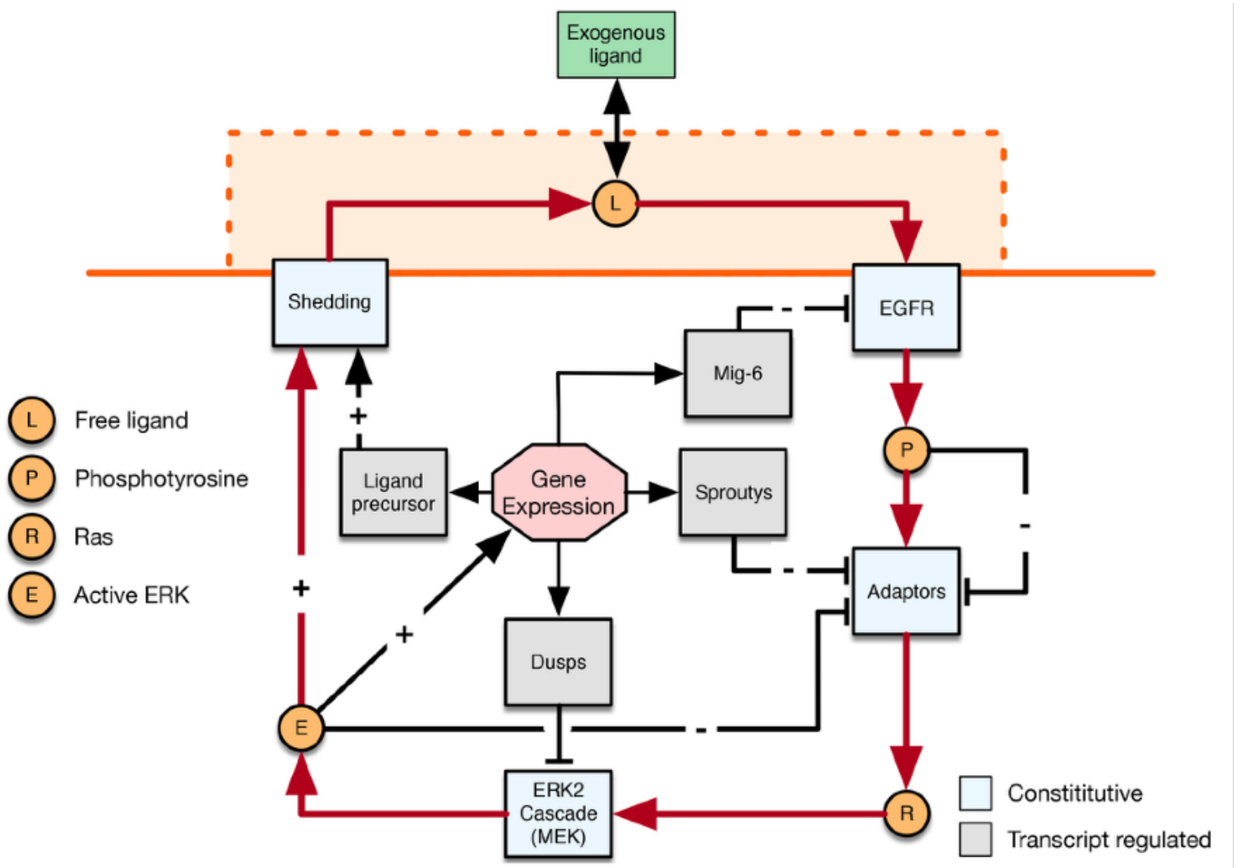
Parameters are mostly undetermined, thus parameter space is large

Omics data captures most (if not all) components but is expensive to characterize dense temporal dynamics.

Dense temporal characterization can be applied to some well-studied signaling proteins.

Experimental data can also be sparse in terms of different conditions, time points, doses, cell types.

Epidermal growth factor receptor (EGFR) signaling with different modules



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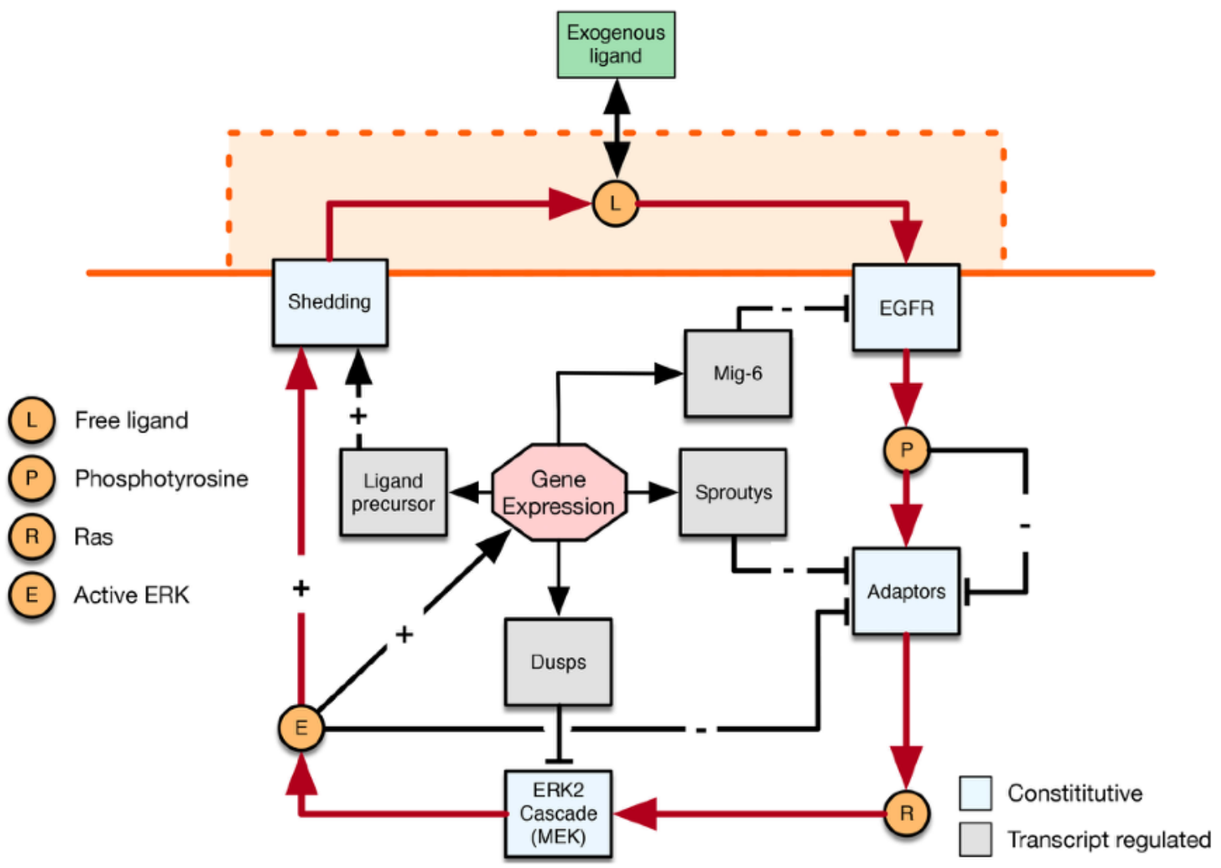

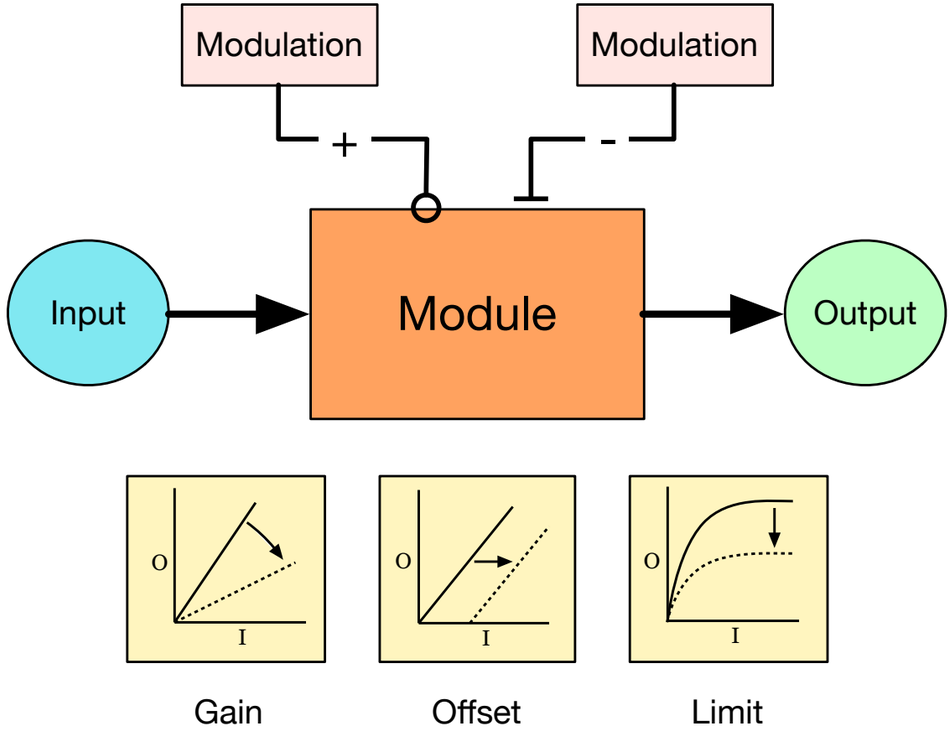

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Rules for parsing networks into modules

- The primary input of each module must be essential for its output
  - Removing the input signal brings the output signal to zero
  - The input must be rate-limiting to its output
- The module output should display low retroactivity (insulation)
  - The output can be irreversible (e.g. proteolysis)
  - Output can be kinetically isolated (e.g. rapid cycling)
  - Output can be >> than downstream inputs
- Each module should be connected to multiple upstream and downstream modules
  - Modules should be multi-purpose and be able to be reused in multiple cellular contexts
- Input-output relationship of modules can be modulated by cross-talk and feedback
  - Modulation can change module gain, offset or maximum output (limit)

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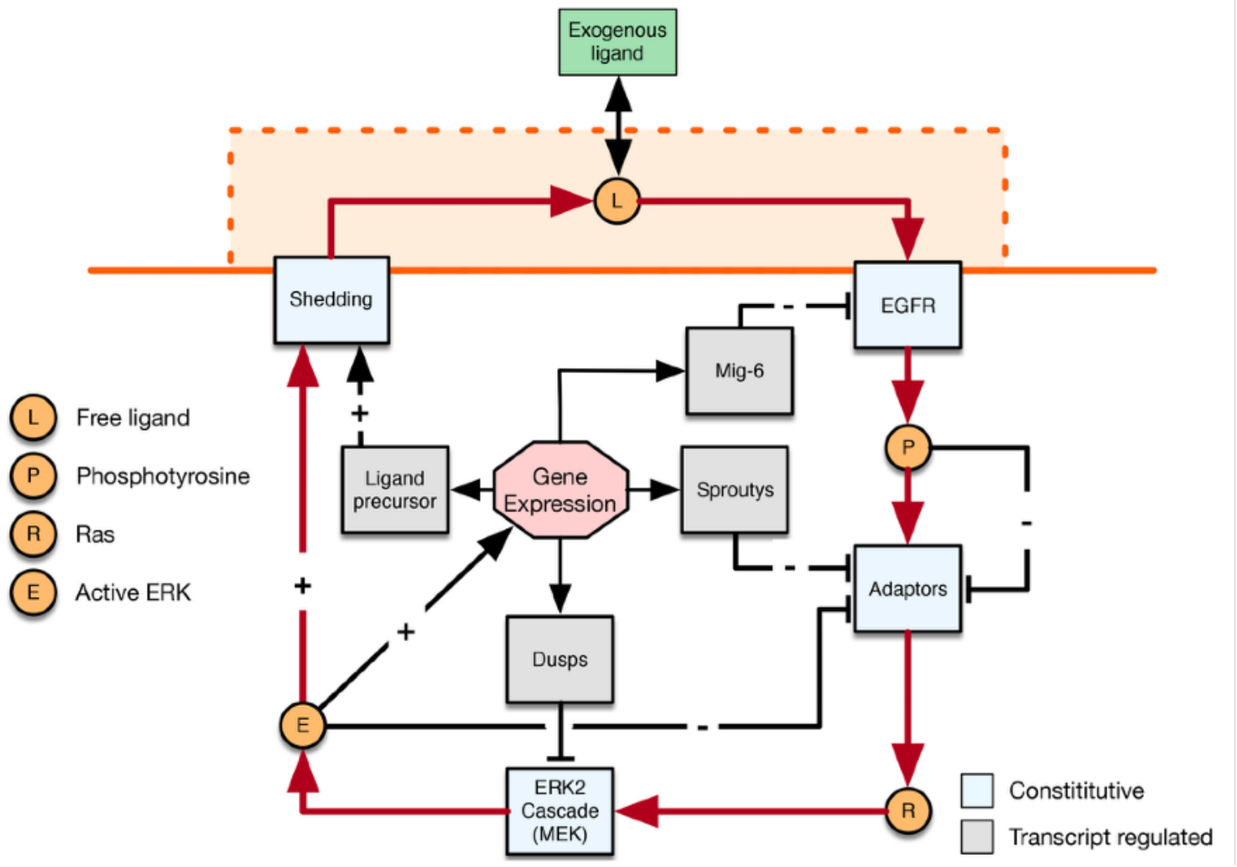

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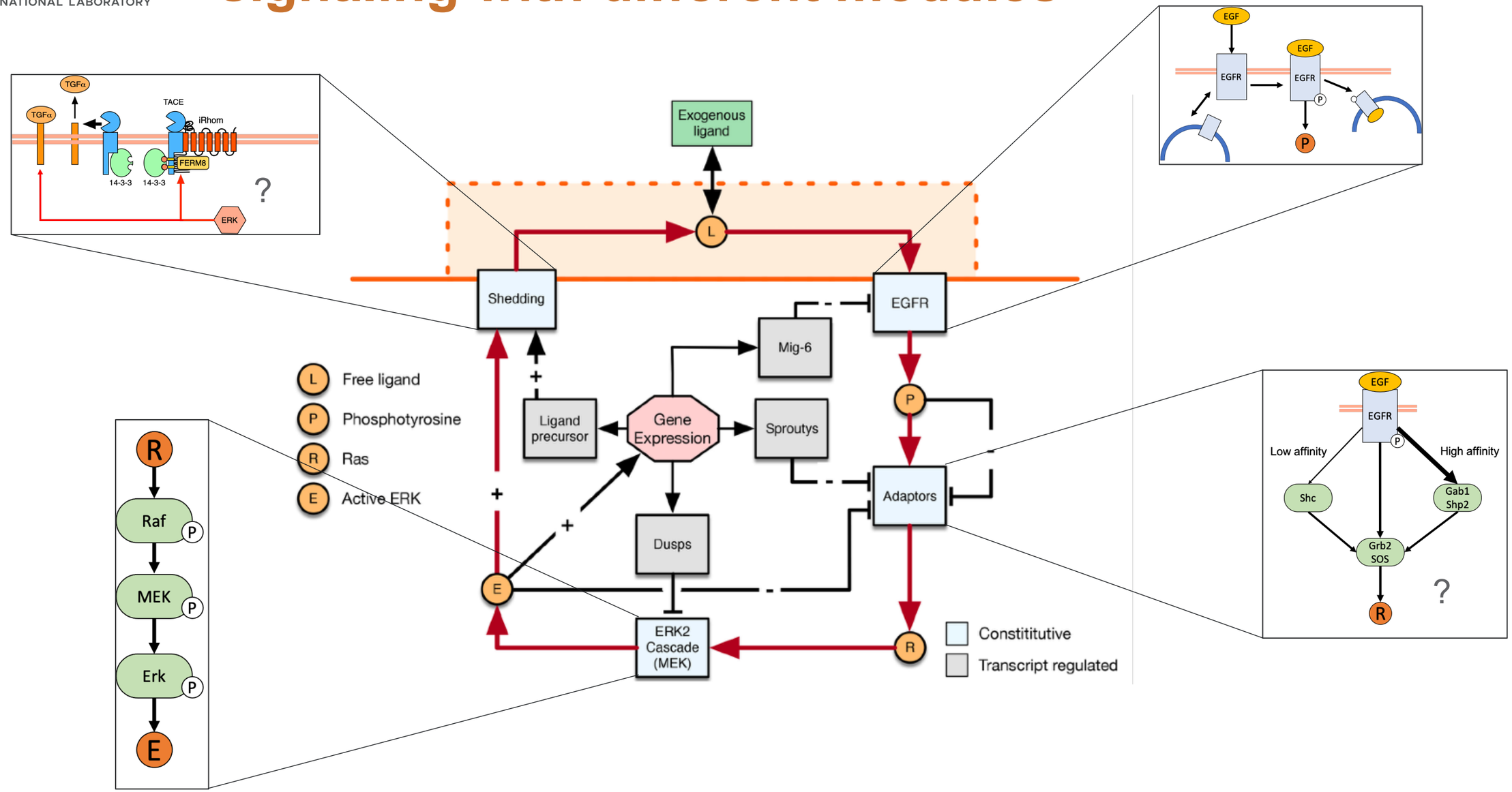
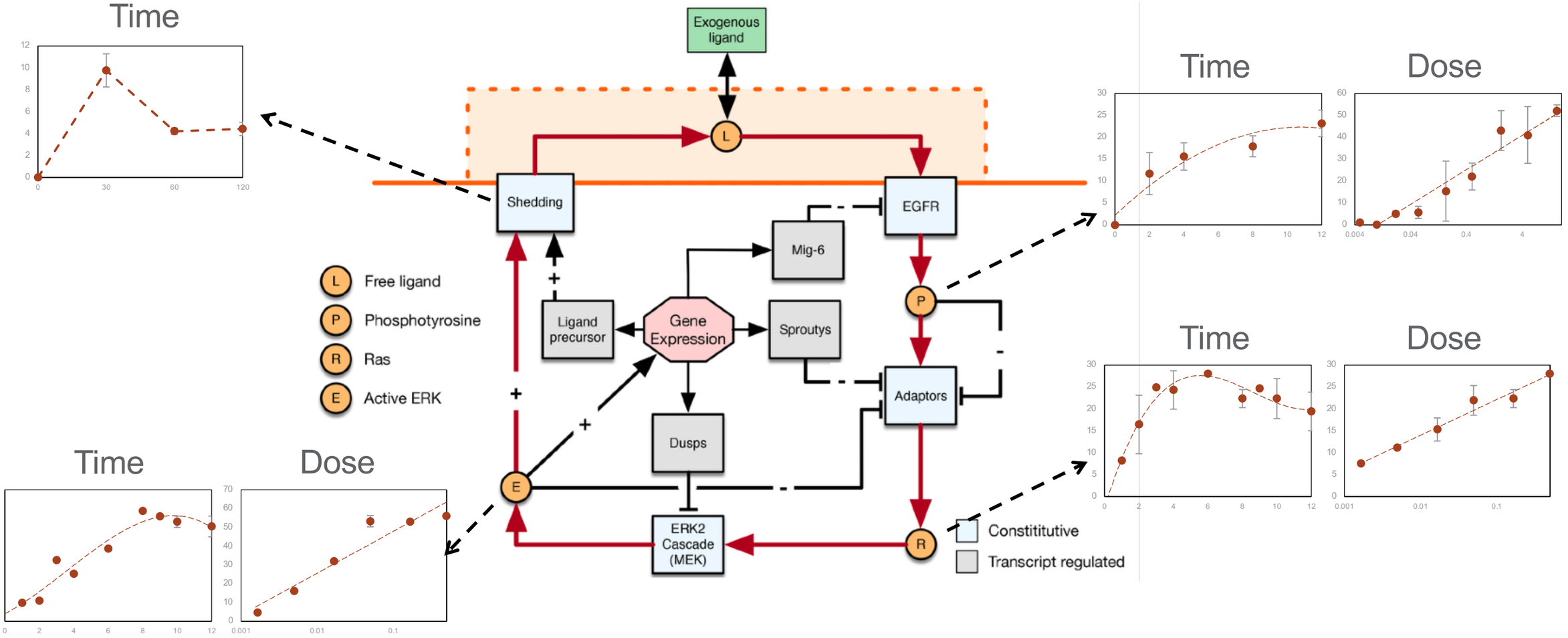
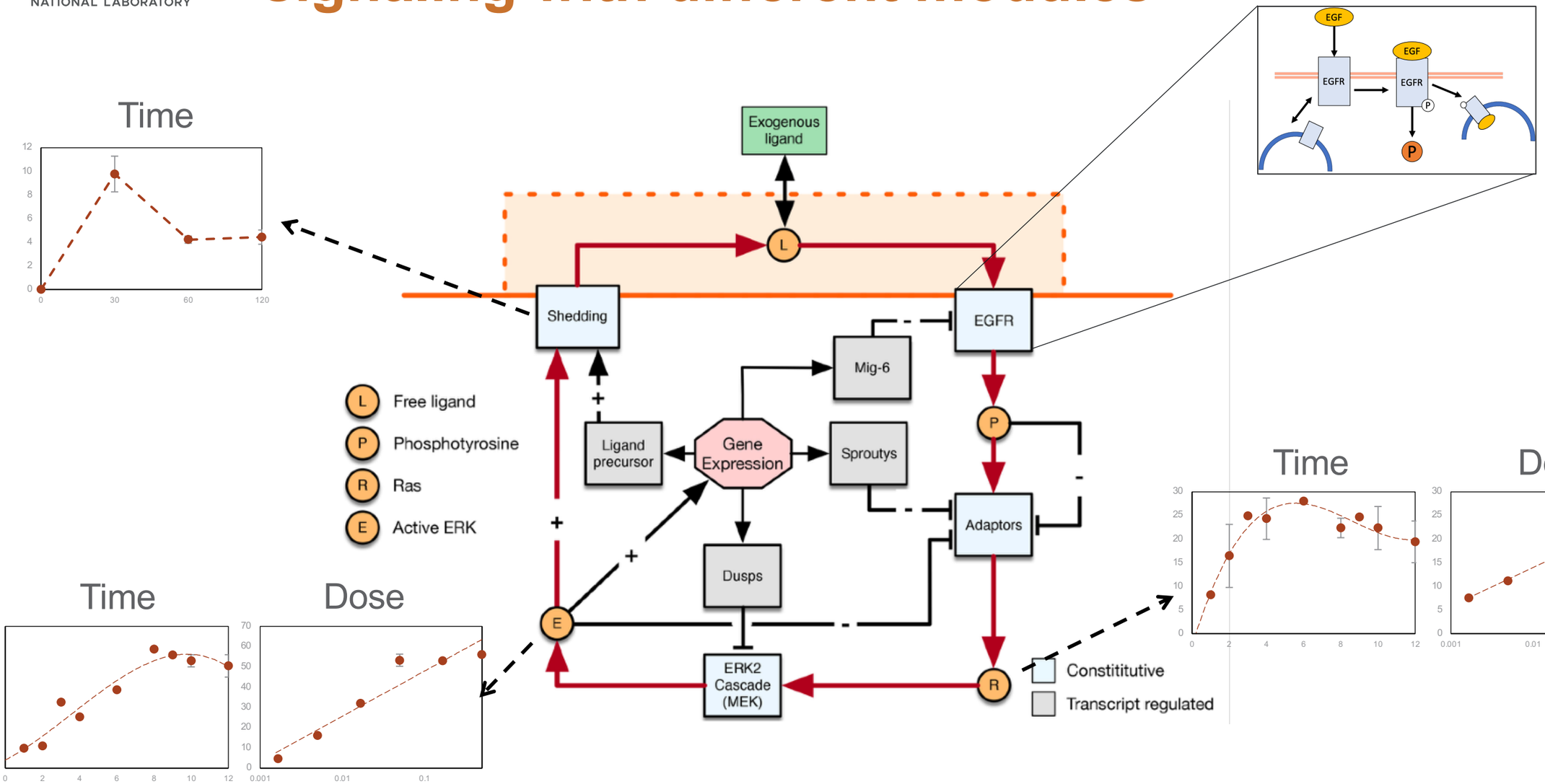


Epidermal growth factor receptor (EGFR) signaling with different modules

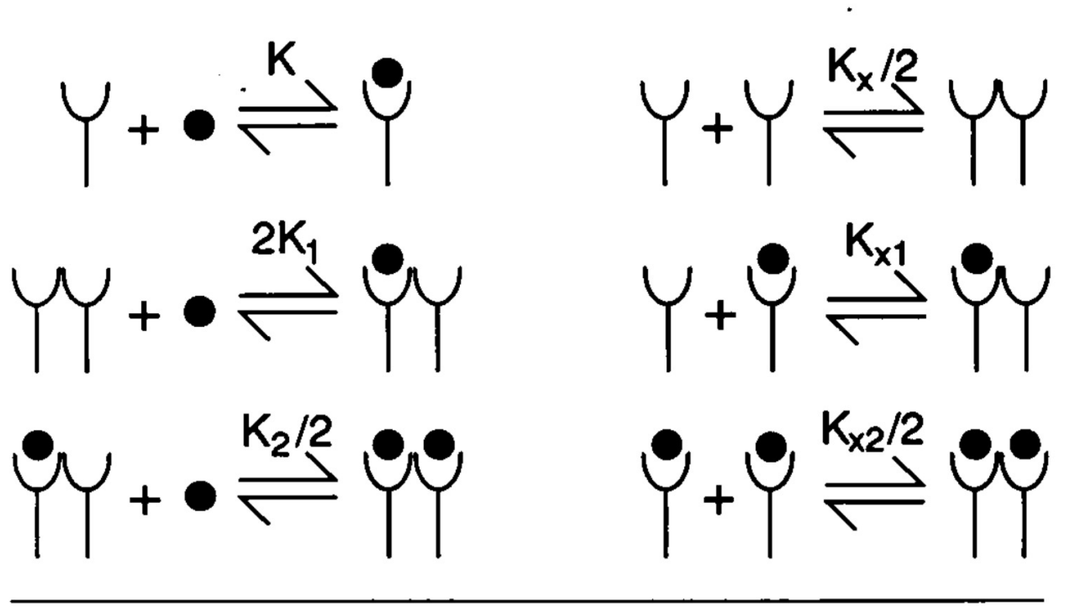


Epidermal growth factor receptor (EGFR) signaling with different modules



You can represent complex biochemistry within each module

Ligand binding and EGFR dimerization




```
// Reactions:
// EGFR module

New_Receptors: => R; Vr;
Receptor_endo: R => Ri; R*ki;
Ligand_binding_0: E + R -> RE; (kf1*R*E - kf1*K1*RE);
Ligand_binding_1: E + RR -> RRE; (kf1/g1*RR*E -
            kf1*K1*g1*RRE);
Ligand_binding_2: E + RRE -> ERRE; (kf1/g2*RRE*E -
            kf1*K1*g2*ERRE);

Ligand_binding_3: E + RRp -> RRpE; (kf1/g1/g3*RRp*E -
            kf1*K1*g1*g3*RRpE);
Ligand_binding_4: E + RRpE -> ERRpE; (kf1/g2/g3*RRpE*E -
            kf1*K1*g2*g3*ERRpE);
Ligand_binding_5: E + RpRp -> RpRpE; (kf1/g1/g3/g4*RpRp*E -
            kf1*K1*g1*g3*g4*RpRpE);
Ligand_binding_6: E + RpRpE -> ERpRpE;
            (kf1/g2/g3/g4*RpRpE*E - kf1*K1*g2*g3*g4*ERpRpE);

Receptor_Dimerization_0: R + R -> RR; (kf2*R*R - kf2*K2*RR);
Receptor_Dimerization_1: RE + R -> RRE; (kf2/g2*R*RE -
            kf2*K2*g2*RRE);
Receptor_Dimerization_2: RE + RE -> ERRE; (kf2/g2/g1*RE*RE -
            kf2*K2*g2*g1*ERRE);
```

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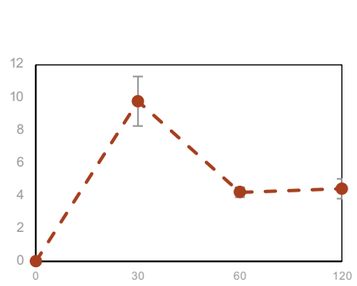
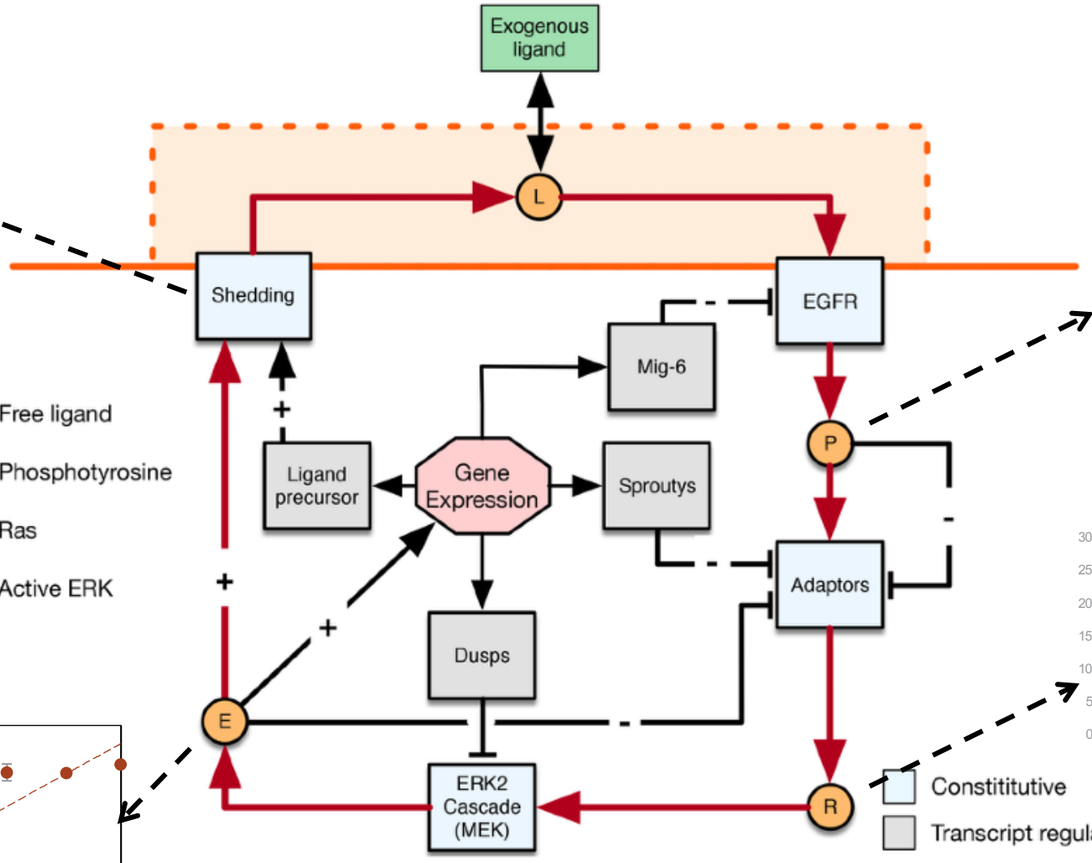


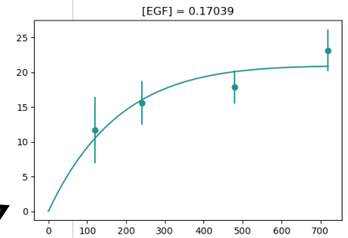


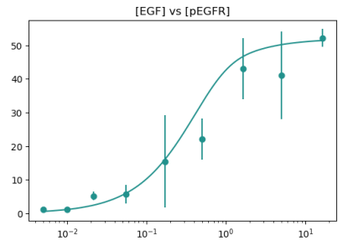
L Free ligand

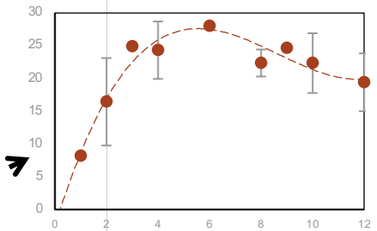
P Phosphotyrosine

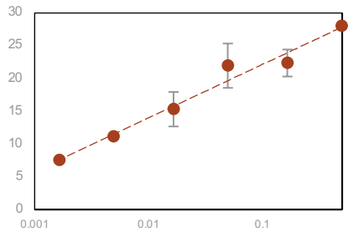
R Ras

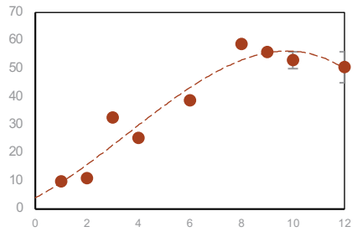
E Active ERK

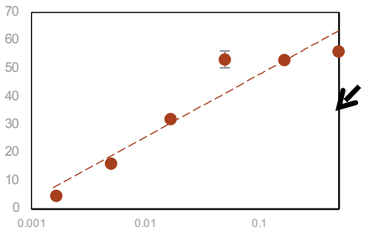








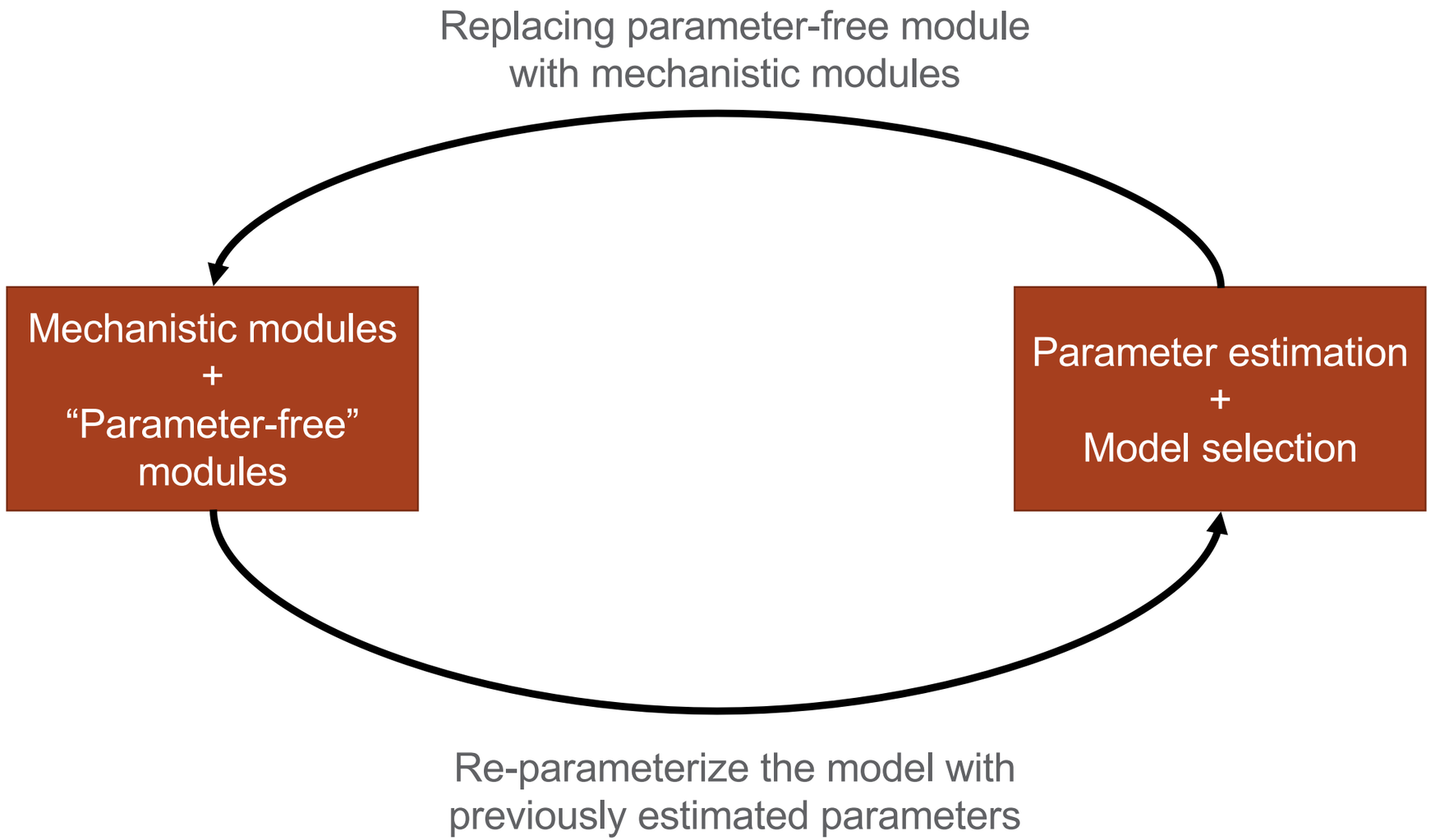




Constitutitutive

Transcript regulated

Hybrid of coarse-grained and fine-grained models



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Thank you