Figure Comments:

1.a.

-- Under the heading ‘Network embedding’ each schematized network is intended to represent a blowout of a single node of the network above it. For example, a single node in the network of organelles (labeled ‘Organelle’) contains the molecular network (labeled ‘Molecule’) below it. This is correctly illustrated for the bottom two networks, but the blowouts for higher order networks appear to have been lost in this revision. (see original Figure 1.a attached).

1.c.

-- It appears that in the network schematic to the furthest right (‘Connection weight’) the paths between nodes in the network no longer have a width that corresponds to the connection weight. Would it be possible to change the thickness of the lines to reflect the connection weight? (see original Figure 1.c. attached)

-- The column labels for the matrices appear to have slightly shifted from center on the columns.

3.

-- There is an underline of Eij in the formula for shortest path distance that can be removed.

4.

-- We accept all changes here. Thank you.

5.

-- We agree that it could be useful to include a key to describe different figure components as you have suggested. The following labels could be applied to the draft legend you provided:

Black arrow - regulatory interaction.

Green arrow - gain of interaction.

Red (dashed) arrow - loss of interaction.

Grey arrow - unmodified interaction.

Blue filled circle - macromolecule.

Blue unfilled circle - unoccupied binding site.

We suggest that because there is no difference in intended meaning between our red dashed arrows and red solid arrows for this figure, all red arrows in this figure be consistently shown as red dashed arrows (or alternatively all red solid arrows).

-- We also noticed that a pair of nodes in the middle panel of 5.a., labeled ‘Rewiring network’, shows a change in direction of the regulatory interaction (gain towards the central node as a green curved arrow and loss away from the central node as a red dashed arrow). However, this change in direction is not reflected in the ‘Diseased regulatory network’ panels. The arrow still points in the same direction as shown in the ‘Normal regulatory network’. Would it be possible to change the direction of this arrow in the ‘Diseased regulatory network’ panels (both top and bottom) to point towards the central node?

6.

-- We accept all changes to this figure. Thank you.

7.b.

-- We agree that a brief description in the caption or figure legend is useful here. Although there is some description in the existing figure caption text, it may be useful to add a visual legend similar 8.d., with two gradient scales/bars corresponding to 1) the information content of nodes in red and 2) the information flux or propagation among nodes in grey (matrix representations).

e.g.:

Information (e.g., disease association)

Low (white) 🡪 High (red)

Information propagation

Low (white) 🡪 High (grey)

8.c.

-- Yes, we accept all changes to this figure. Thank you.

9.

-- Yes, we agree that providing these insights as short phrases may improve clarity here. From left to right we could replace existing text with the following four short phrases:

The E. coli GRN has a robust network architecture, different from software systems designed for efficient reuse of basic functions. (131)

Unexpectedly close connections among immune cell types may occur similar to how individuals can be well connected through shared relationships. (8, 133)

Flight routes tend to route through hub airports in a rich-get-richer phenomenon. Likewise, molecular substrates such as pyruvate can function as metabolic hubs. (136, 137)

Electrical distribution networks reflect geographic constraints while protein interaction networks may be constrained by 3-dimensional spaces inside cells. (139)