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## Biophysics of disordered nuclear receptors and their DNA binding regulation

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# Stellingen

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## Biophysics of disordered nuclear receptors and their DNA binding regulation

1. For intrinsically disordered protein regions, where function is an emergent property of the dynamic ensemble, the classical structure-function paradigm is insufficient and should be replaced by a dynamics-function paradigm.  
*This thesis*
2. A mechanistic understanding of dynamic protein systems is likely only achievable through an integrative approach that combines the predictive power of computational modelling with the empirical validation of experimental methods.  
*Adapted from A. Musacchio, EMBO J. (2022)*
3. The pathology of the polyglutamine-expanded androgen receptor is not a classical misfolding event, but a dynamic misfolding that globally perturbs the conformational ensemble of its disordered N-terminal domain.  
*This thesis*
4. The structural plasticity of intrinsically disordered domains represents a key therapeutic frontier for developing allosteric modulators that can fine-tune, rather than simply inhibit, cellular signalling pathways.  
*Adapted from Lazar et al., Nat. Rev. Drug. Discov. (2025)*
5. The orphan status of the nuclear receptor Nur77 is challengeable: they can be liganded by small molecules which tune and re-direct their DNA target specificity rather than simply switching them *on* or *off*.  
*This thesis*
6. The principles of IDR-mediated modulation of transcription factor residence time on DNA may provide a fundamental biophysical framework for building predictive models of biomolecular condensate regulation.  
*Adapted from Garcia et al, Mol. Cell (2021)*

7. *In vitro* single-molecule biochemical and biophysical assays are indispensable not as a final representation of cellular reality, but as a method to establish a quantitative baseline of a protein's properties.  
*This thesis*
8. It is critical for a new scientific field to move beyond phenomenology by developing an integrative framework that converts descriptive observations into predictive principles valid from single molecules to multicellular systems.  
*Adapted from Alberti et al., Nat. Commun. (2025)*
9. Scientists bear the responsibility of articulating, rather than obscuring, the nuance and complexity that defines biological systems.  
*Adapted from D. Noble, Nature (2024)*
10. Major scientific breakthroughs do not just expand the boundary of what we know, they fundamentally establish our understanding of what we do not.
11. The current revision of our understanding of proteins and protein regions exemplifies Albert Szent-Györgyi's statement that research is to see what everybody has seen and think what nobody has thought.
12. There is a Socratic acceptance of the limits of one's own knowledge, and then there is ignorance.

**Laurens W.H.J. Heling**

Leiden, 25 juni 2026