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Transformação Digital
e Práticas Inovadoras na Educação e Saúde Pública :
para um Futuro sustentável

IN SILICO METHODS FOR DRUG DEVELOPMENT IN NEGLECTED DISEASES: OPPORTUNITIES FOR PUBLIC HEALTH INNOVATION

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ABSTRACT

Neglected tropical diseases (NTDs) impose a substantial burden in low- and middle-income countries while attracting limited investment and innovation. Digital transformation has enabled *in silico* approaches that accelerate discovery by integrating structural biology, cheminformatics, and machine learning. This chapter analyzes how computational pipelines support target identification, virtual screening, molecular dynamics, pharmacophore and QSAR modeling, as well as ADMET prediction, with case studies in Chagas disease, leishmaniasis, schistosomiasis, and arboviruses. We discuss the role of open databases and collaborative platforms, including TDR Targets, ChEMBL, DrugBank, and open-source initiatives, and outline future directions where AI and multi-omics integration can reduce time, cost, and risk in public-health-oriented drug discovery.

KEYWORDS: Artificial Intelligence; Drug Discovery; Neglected Tropical Diseases; Public Health

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1. Neglected Diseases as a Public Health Priority

NTDs such as Chagas disease, leishmaniasis, schistosomiasis, onchocerciasis, and arboviruses collectively affect more than one billion people and contribute millions of DALYs worldwide[1,3]. Their prevalence is concentrated in settings with limited sanitation, vector control, and access to healthcare, which amplifies cycles of poverty and social stigma[1]. Despite this burden, most therapeutic options remain decades old and are often toxic or operationally complex; benznidazole retains limited efficacy in chronic Chagas cardiomyopathy, and amphotericin B for leishmaniasis demands inpatient care with nephrotoxicity risk[4,5].

The resulting innovation gap reflects a structural paradox: diseases of high public-health importance but low commercial return receive less R&D investment[6]. WHO roadmaps emphasize elimination targets and the linkage between NTD control and Sustainable Development Goals, yet implementation lags in many endemic regions[3]. In this context, *in silico* methods can lower barriers by reducing wet-lab costs, prioritizing hypotheses, and fostering cross-border collaboration through digital platforms[2,18]. Computational pipelines thereby become instruments not only of scientific efficiency but also of health equity.

2. Principles and Tools of *In Silico* Drug Discovery

2.1 Target identification and validation

Rational discovery begins with targets that are essential for pathogen survival and ideally absent or divergent in humans. Comparative genomics and proteomics help nominate enzymes in parasite-specific pathways, while structural analyses assess druggability by locating well-defined pockets[7]. In trypanosomatids, trypanothione reductase and cruzain exemplify validated targets with extensive structural and biochemical characterization[13,14]. Public repositories and pathogen-focused portals, such as TDR Targets, streamline this step by integrating omics, essentiality, and annotation metadata[17].

2.2 Virtual screening and molecular docking

Virtual screening narrows chemical space by ranking large libraries against predicted binding sites. Docking engines estimate binding poses and interaction energies, enabling triage before biochemical testing[2,8]. For *Trypanosoma cruzi*, docking informed the repurposing of azole antifungals against sterol 14α-demethylase and guided design of cruzain inhibitors with improved complementarity to the catalytic cleft[13]. Although docking is computationally efficient, its accuracy depends on input structures, protonation states, and treatment of receptor flexibility[2,8].

2.3 Molecular dynamics simulations

Molecular dynamics (MD) complements docking by modeling atomistic trajectories under explicit solvent, capturing induced fit, water networks, and conformational selection[9]. In leishmaniasis, MD helped discriminate stable complexes of trypanothione reductase inhibitors and rationalize structure–activity relationships[14]. Free-energy methods such as MM/GBSA and alchemical calculations refine affinity estimates, improving enrichment after docking[9].

2.4 Pharmacophore modeling and QSAR

Pharmacophore models encode spatial arrangements of essential features observed in active ligands, enabling scaffold hopping and focused library design[10]. QSAR maps molecular descriptors to bioactivity, yielding predictive models that prioritize analogs for synthesis and testing. For natural-product scaffolds with antileishmanial potential, pharmacophore-guided optimization has accelerated the selection of drug-like chemotypes[14].

2.5 ADMET and safety profiling

Computational prediction of absorption, distribution, metabolism, excretion, and toxicity eliminates liabilities early, conserving resources[11]. In NTD pipelines where formulation and field deployment are challenging, *in silico* flags for solubility, permeability, hERG risk, CYP interactions, and hepatotoxicity help align candidates with public-health realities such as oral dosing and minimal monitoring[11].

2.6 Machine learning and AI integration

Deep learning enhances scoring, pose prediction, and de novo design by learning non-linear structure–activity patterns from large chemogenomic datasets[12]. During outbreaks, AI-assisted repurposing can rapidly sift through approved drugs and clinical-stage compounds to identify candidates against viral enzymes[16,20]. When coupled with multi-omics, AI also reveals host–pathogen network vulnerabilities that support multitarget or host-directed strategies[19].

3. Applications and Case Studies in Neglected Diseases

3.1 Chagas disease

For *T. cruzi*, cruzain and sterol biosynthesis enzymes dominate the target landscape. Structure-based campaigns integrated docking, MD, and medicinal chemistry to deliver submicromolar cruzain inhibitors with balanced physicochemical profiles[13]. Docking also supported azole repurposing against CYP51, informing translational efforts; however, mixed clinical outcomes underscore the need for combination regimens and precise patient stratification[4,13]. Proteomic analyses continue to reveal metabolic chokepoints that can be exploited for polypharmacology[7].

3.2 Leishmaniasis

Computational screening against trypanothione reductase and dihydrofolate reductase identified chemotypes later validated in biochemical and cellular assays[14]. Pharmacophore modeling facilitated optimization of natural products, while MD rationalized differences in potency via pocket hydration and loop dynamics[14]. Because clinical management varies by *Leishmania* species and clinical form, prioritizing broad-spectrum targets with conserved pockets is a strategic aim[14].

3.3 Schistosomiasis

With praziquantel as the lone frontline therapy, resistance concerns motivate discovery of new mechanisms. Target-centric docking against thioredoxin–glutathione reductase and proteases has nominated repurposed drugs and novel series with in vitro activity[15]. Computational analog design around the

praziquantel scaffold seeks to modulate stereochemistry and physicochemical parameters to improve spectrum and reduce dose requirements[15].

3.4 Arboviruses (dengue and related flaviviruses)

NS3 protease and NS5 polymerase are archetypal antiviral targets. Structure-guided docking and MD prioritized nucleoside and non-nucleoside scaffolds, while AI-assisted repurposing rapidly surfaced pan-flavivirus candidates during recent epidemics[16,20]. Cross-reactivity modeling helps predict broad-spectrum potential, an asset for regional programs facing cocirculation of multiple arboviruses[16].

4. Digital Platforms, Collaboration, and Artificial Intelligence

Open databases democratize access to high-quality chemical and biological data. ChEMBL and PubChem provide bioactivity and structure repositories; DrugBank curates drug–target relationships and pharmacology; TDR Targets integrates parasite genomics with pathogen-specific annotations[17]. These resources allow groups in endemic regions to launch *in silico* projects without prohibitive licensing costs[17].

Collaborative initiatives such as Open Source Drug Discovery and DNDi operationalize distributed discovery, blending computational prioritization with experimental validation across partner labs[18]. Such models are well-suited to NTDs, where public-private partnerships and not-for-profit portfolios dominate.

Artificial intelligence enhances each stage of the pipeline. Deep generative models propose synthetically accessible molecules that satisfy potency and ADMET constraints[12]. Active-learning loops couple predictive models with iterative testing, improving hit rates while reducing assays. Integration with multi-omics clarifies host–pathogen dependencies, revealing opportunities for host-directed or multitarget therapies[19]. During emergencies, cloud-based platforms enable rapid virtual screening and consensus modeling for repurposing campaigns[16,20].

Ethical and policy considerations remain central. Open science commitments should include capacity building in computational chemistry and data stewardship to ensure equitable participation by institutions in

endemic countries. Data governance must protect patient privacy when clinical datasets inform AI models, while preserving FAIR principles to maximize reuse.

5. Future Directions and Integration into Health Systems

Hybrid discovery models will combine *in silico* prioritization with high-content phenotypic screening and orthogonal biophysics, shortening cycle times and attrition[2,8,9]. Standardized reporting of docking protocols, MD settings, and validation metrics will improve reproducibility and regulatory confidence. As agencies progressively accept modeling and simulation data, computational evidence will carry greater weight in preclinical packages, particularly for repurposing and mechanism-of-action support.

Sustainability considerations favor computational pipelines: fewer reagents, reduced waste, smaller animal usage, and lower costs align with environmental and ethical goals[11]. Embedding digital discovery capabilities within national reference laboratories and university networks can create regional innovation hubs that respond quickly to outbreaks and endemic-disease priorities.

Ultimately, translation requires linkage to surveillance, diagnostics, and access programs. *In silico* efforts should be coupled to target product profiles that reflect field constraints, including oral dosing, heat-stable formulations, and short treatment courses. By aligning computational innovation with public-health logistics, countries can advance toward equitable control and elimination targets for NTDs[3].

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