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Review Article

Calcium-mediated mitochondrial energy deficiency in Parkinson's and Alzheimer's diseases: Insights from computational modelling

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Alzheimer's and Parkinson's diseases are the most prevalent neurodegenerative disorders worldwide and are characterised by progressive cognitive and functional impairments caused by neuronal loss. Energy deficiency is a predominant hallmark of their pathophysiology and plays a central role in the development of the disease, notably by mitochondrial dysfunction enhancing protein aggregation and oxidative stress which trigger subsequently immune responses and neuronal loss. Quantifying this energetic deficiency and identifying specific causative mechanisms from the complex network of interacting metabolic and regulatory pathways at play is rather challenging, where integrative mathematical modelling represents a powerful tool to support these investigations. Here, we review the latest developments in integrative modelling in brain bioenergetics in relation to Alzheimer's and Parkinson's diseases where we focus on the regulatory role of Ca^{2+} signalling. Finally, we discuss recent challenges and future directions to improve the current understanding of the energy-deficiency theory of neurodegeneration.

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Introduction

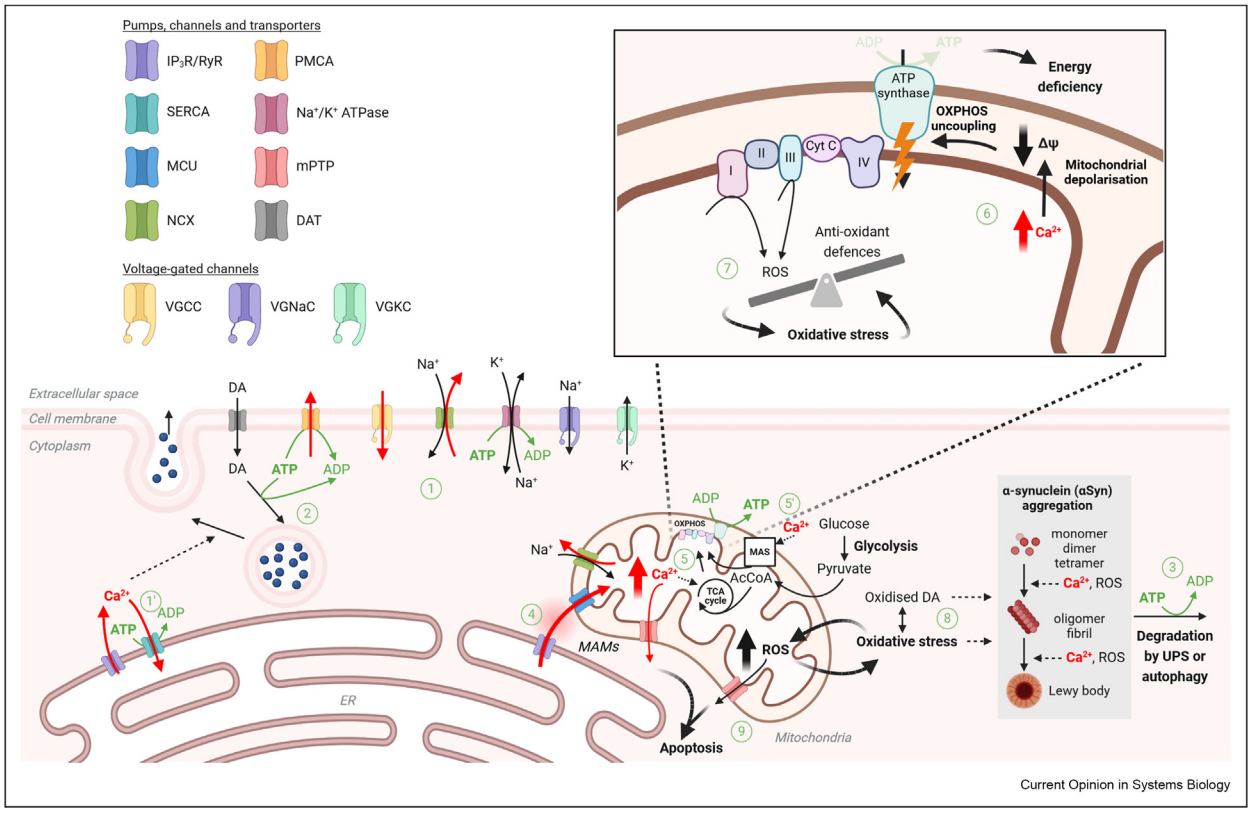
Alzheimer's disease (AD) and Parkinson's disease (PD) are recognised as the most prevalent neurodegenerative disorders worldwide. Symptomatic relief can be achieved with the currently available treatments, but a sustainable cure for those diseases has so far not emerged [1,2]. Both diseases are characterised by cognitive decline and functional impairments caused by neuronal death in specific brain regions, and are associated with protein accumulation in the brain, neuroinflammation, brain atrophy, increased oxidative stress, mitochondrial dysfunction, remodelling of glucose metabolism and dysregulation of Ca^{2+} dynamics [1,2].

It is now widely accepted that the accumulation of α-synuclein in PD or of amyloid β (Aβ) and neurofibrillary tangles composed of hyperphosphorylated tau proteins in AD leads to various anomalies and eventually to neurodegeneration [2,3]. The characteristic motor symptoms of PD mainly result from the death of dopaminergic neurons in the *substantia nigra pars compacta* (SNc) [2] whereas memory loss in AD is attributed to impairments in synaptic transmission and notably to the degeneration of cholinergic neurons in the basal forebrain [1]. Accumulating evidence also points to a remodelling of cellular interactions across the brain cell network in both AD and PD, and highlights the potential contribution of non-neuronal cells such as astrocytes and microglia [4–6]. These glial cells secrete various molecules (gliotransmitters, cytokines, chemokines *etc.*) that not only regulate synaptic transmission and plasticity, but also control brain inflammatory responses [5,7]. Anomalous release/uptake of these molecules, dysfunctional signal transduction or sustained release of pro-inflammatory cytokines, with their potential amplification by excess protein aggregates, constitute major causes of neurotoxicity and neuronal death [5,8].

Nevertheless, the exact sequence of events driving neurodegeneration remains elusive. Aging, genetic mutations and exposure to environmental toxins cause many disturbances in physiology that could act upstream of protein deposition [9]. Among those, impaired bioenergetics, characterised by adenosine triphosphate (ATP) deficiency, stands out as another early and robust hallmark of neurodegeneration [9]. Various signalling and housekeeping processes that are essential to proper synaptic function and neuron homeostasis require ATP [10,11]. For instance, the maintenance of the resting membrane potential and the encapsulation of neurotransmitters in vesicles are mediated by ATPases. Alterations in different metabolic, signalling or transport pathways, notably reducing glucose uptake and mitochondrial efficiency, compromise ATP production while maintaining (or even increasing) the neuronal energy demand (Figure 1). Moreover, neuroinflammation triggers a metabolic rewiring in microglia [12,13] that limits glucose and lactate availability in the tissue and could potentially induces ATP deficiency in neurons [14]. Targetting the aforementioned pathways (Figure 1) to prevent ATP deficiency thus appears as a promising strategy for therapeutic intervention [15].

However, understanding the mechanisms of disease onset and progression appears as an intractable problem if

Figure 1



Energetic and Ca^{2+} contributions to the onset and progression of PD. The homeostasis of SNc dopaminergic neurons is associated with a high energetic cost due to the following main mechanisms. (1)/(1′) Action potentials are accompanied by large Ca^{2+} entry through VGCC and recovery is mediated by ATPases (PMCA, SERCA, Na^+/K^+ ATPase). (2) DA encapsulation in vesicles is enabled by the vesicular monoamine transporter, a V-ATPase. The vesicle recycling (not shown) also involves a V-ATPase. (3) Damaged protein disposal mechanisms mediated by UPS and lysosomes require ATP (ubiquitination, ATP-dependent proteasome and lysosomal V-ATPase). (4) The Ca^{2+} influx induced by VGCC is amplified by IP_3Rs and RyRs through a process of Ca^{2+}-induced Ca^{2+} release and readily taken up by mitochondria due to the close proximity between these channels and the MCU in MAMs. (5)/(5′) High Ca^{2+} level stimulates mitochondrial NADH availability by activating the TCA cycle (5) or *via* the MAS (5′). NADH enters the ETC which establishes the proton motive force driving the synthesis of ATP by ATP synthase. The intense stimulation of OXPHOS tends to build up a basal oxidative stress due to the production of ROS. (6) Under some circumstances (e.g. PD-related mutations, mitochondrial dysfunction *etc.*), altered mitochondrial Ca^{2+} exchanges lead to Ca^{2+} overload, which decreases the mitochondrial membrane potential and uncouples the ETC from ATP production. The disruption of mitochondrial ATP synthesis is a major cause of **energy deficiency**. (7) ROS production increases due to the overstimulation of the ETC by Ca^{2+} and the anti-oxidant defence system becomes overwhelmed. The resulting oxidative stress is self-amplified by the mitochondrial damage caused by ROS, which further alters the activity of the ETC. (8) The leakage of ROS to the cytosol activates dopamine oxidation. The presence of oxidised dopamine as well as high ROS and Ca^{2+} levels favours the aggregation of αSyn into oligomers and Lewy bodies. Importantly, energy deficiency prevents the alleviation of these stress conditions by dopamine encapsulation (2), Ca^{2+} removal (1)/(1′) or protein degradation (3), which are all ATP-dependent. (9) Ca^{2+} and ROS accumulation in mitochondria finally induces the opening of mPTP, which triggers an apoptotic signalling cascade (caspase) leading to neuronal death. (Red and black dashed arrows represent Ca^{2+} fluxes and direct activation of another process, respectively.)

we consider the highly intricate network of intra- and intercellular regulation pathways controlling the ATP level (Figure 1) [15]. Mathematical modelling has emerged as a powerful tool to address those challenges by providing modular and integrative approaches [16] where the response of a core brain energy model [17] to individual disease-related mechanisms [18] can be analysed. Here, we review the developments from the past 10 years in integrative modelling of brain cellular bioenergetics and focus on the mechanistic models capturing AD- and PD-related alterations with an emphasis on Ca^{2+} homeostasis. Models of astrocyte and neuron metabolism [19], of AD and PD pathogenesis [20,21] or of mitochondria in health and neurodegeneration [22] have been extensively reviewed elsewhere.

After presenting the major classes of models with their scope and limitations, we elaborate on how to integrate them in frameworks to more systematically quantify energetic damage in neurodegeneration or envision multiscale and translational models.

Overview of recent mechanistic models of brain cell energetics

PD models

The shape of dopaminergic neurons in the SNc has been proposed to lead to their intrinsic vulnerability, due to the mismatch between their energy budget, on the one hand, and the energetically demanding large number of synaptic connections and size of their unmyelinated axonal architecture, on the other hand [23,24]. Morphological and electrophysiological models of those cells have shown that the propagation and recovery from an action potential represent extremely large energy demands that could probably not be balanced in unhealthy cells with dysfunctional metabolism [25,26].

The autonomous pacemaking of SNc dopaminergic neurons, *i.e.* their ability to sustain continuous spiking without synaptic excitatory stimulus, leads to the repetitive opening of voltage-gated Cav1 Ca^{2+} channels (VGCC L-type Ca^{2+} channels) and to high-amplitude oscillations in Ca^{2+} concentration [27,23,24]. The low cytosolic Ca^{2+} buffering capacity of these neurons is a double-edge sword. Low buffering favours Ca^{2+} accumulations that promote the aggregation of α-synuclein [27,23,24] or trigger apoptotic signals *via* the opening of the mitochondrial permeability transition pore (mPTP) [23]. However, high-amplitude Ca^{2+} spikes have a major impact on the cellular energy balance, not only due to the energetic cost of Ca^{2+} extrusion, but also through the activatory effect of Ca^{2+} on OXPHOS [28,29] (Figure 1). This regulation proceeds either through direct activation of mitochondrial dehydrogenases of the tricarboxylic acid (TCA) cycle, which relies on Ca^{2+} transport *via* the mitochondrial Ca^{2+} uniporter (MCU) and enhances the flux of the electron transport (ETC) chain, or is mediated by the Ca^{2+}-regulated Aralar/Malate-Aspartate shuttle (MAS), involved in NADH transport from the cytosol to mitochondria [30,31].

Some PD-related mutations affect the expression of mitochondrial Ca^{2+} transporters, leading to perturbed Ca^{2+} exchanges, Ca^{2+} overload, mitochondrial depolarisation and inefficient coupling between electron transfer and ATP synthesis. Soman et al. have computationally predicted that decreasing the flux through MCU prevents mitochondrial Ca^{2+} overload and restores mitochondrial respiration in neurons carrying a PTEN-induced putative kinase 1 (PINK1) mutation, which was also confirmed experimentally [32]. Silencing or pharmacological inhibition of MCU rescued dopaminergic neurons of zebrafish embryos affected by PINK1 loss-of-function [32]. Their non-spatial computational model captured the cross-talk between Ca^{2+} dynamics and metabolism by key steps of cytosolic and mitochondrial glucose metabolism, regulated by Ca^{2+} exchanges between the cytosol, the endoplasmic reticulum and mitochondria.

Notably, Soman et al. neglected the neuronal membrane electrophysiology and the level of reactive oxygen species (ROS) was not measured nor modelled [32]. However, the excessive production of ROS is a direct consequence of disrupted mitochondrial respiration and the cause of serious cellular damage, ranging from oxidation of essential biomolecules (proteins, lipids, DNA) to impairments in mitochondrial function and quality control [23]. In fact, the chronic exposure of SNc dopaminergic neurons to high ROS levels also contributes to their vulnerability [23]. Indeed, the feedforward activation of OXPHOS by Ca^{2+}, although key in the maintenance of autonomous pacemaking [30], tends to produce high levels of ROS in physiological conditions and thereby generates a basal oxidative stress [33]. Depending on the intracellular redox conditions, the tight interplay between Ca^{2+} and ROS promotes beneficial cell signalling or amplifies abnormal behaviours in pathological conditions [34–36]. Whether the loss of these optimal intracellular redox conditions triggers PD onset remains overall elusive [35].

Models capturing the Ca^{2+}-dependent electrophysiology, redox balance and metabolism of dopaminergic SNc neurons are thus essential to estimate the actual gap between energy supply and demand in those cells. A recent model supporting an energy-deficiency hypothesis for PD pathogenesis [37] constitutes a promising baseline. This model accounts for the dynamics of membrane potential and ionic membrane currents, Ca^{2+} dynamics, glucose metabolism, dopamine metabolism and (Ca^{2+}-dependent) release, ER-stress-induced apoptotic pathways as well as pathways specific to the pathophysiology of PD, adapted from the pioneering work of Cloutier and Wellstead [18]. Briefly, this PD module captures α-synuclein metabolism, protein

degradation pathways, oxidative stress and ROS clearance through the anti-oxidative pathway, with a feedback loop between ROS and α-synuclein dynamics. Energetic costs, expressed in terms of ATP consumption rate, are associated to the propagation and recovery from action potentials, synaptic vesicle management, Ca^{2+} pumping and degradation of damaged proteins.

Hypoglycemic and hypoxic conditions induce energy deficiency, *i.e.* low ATP availability, which limits the degradation of misfolded and aggregated α-synuclein, favours the accumulation of ROS and Ca^{2+} and induces a vicious cycle between ROS, Ca^{2+}, dopamine and α-synuclein dynamics (Figure 1). Experimental evidence of this feedback cycle (comprehensively reviewed elsewhere [38]) supports a multiple hit hypothesis for PD. Although data do not point directly to hypoxia or hypoglycemia as the trigger of the pathological cascade, these conditions might mimic critical upstream perturbations, such as mitochondrial oxidative stress [39]. Of note, similar energy deficiency issues were reported with a simpler computational model of glucose and redox metabolism, and validated against metabolomics measurements from a Parkin knockout mice brain [40]. While Muddapu et al. focussed on energy deficiency, their mathematical model contains the necessary components to formulate different starting hypotheses (e.g. on redox conditions, status of antioxidant defences, mitochondrial Ca^{2+} load, status of mitochondrial respiration *etc.*), which could help clarify the chronology and interdependencies of dysfunctions in the pathogenesis of PD.

This integrative model could be extended with the Ca^{2+} regulation of mitochondrial metabolism to account for Ca^{2+}-induced metabolic adaptations in response to an action potential. Further model refinements could include the MAS, the Ca^{2+} regulation of mPTP and the modelling of mitochondria-associated membranes (MAMs) [41]. The spatial extent of those cytosolic domains, where the ER is in close interaction with the outer mitochondrial membrane, is modified in PD and in AD, thereby altering Ca^{2+} exchanges and, possibly, mitochondrial ATP synthesis [42]. Finally, introducing the interactions with other cells such as astrocytes and microglia to reproduce a tri- or quad-partite synapse would improve the physiological relevance of the model, as discussed in Section From sub-organellar to systems scales.

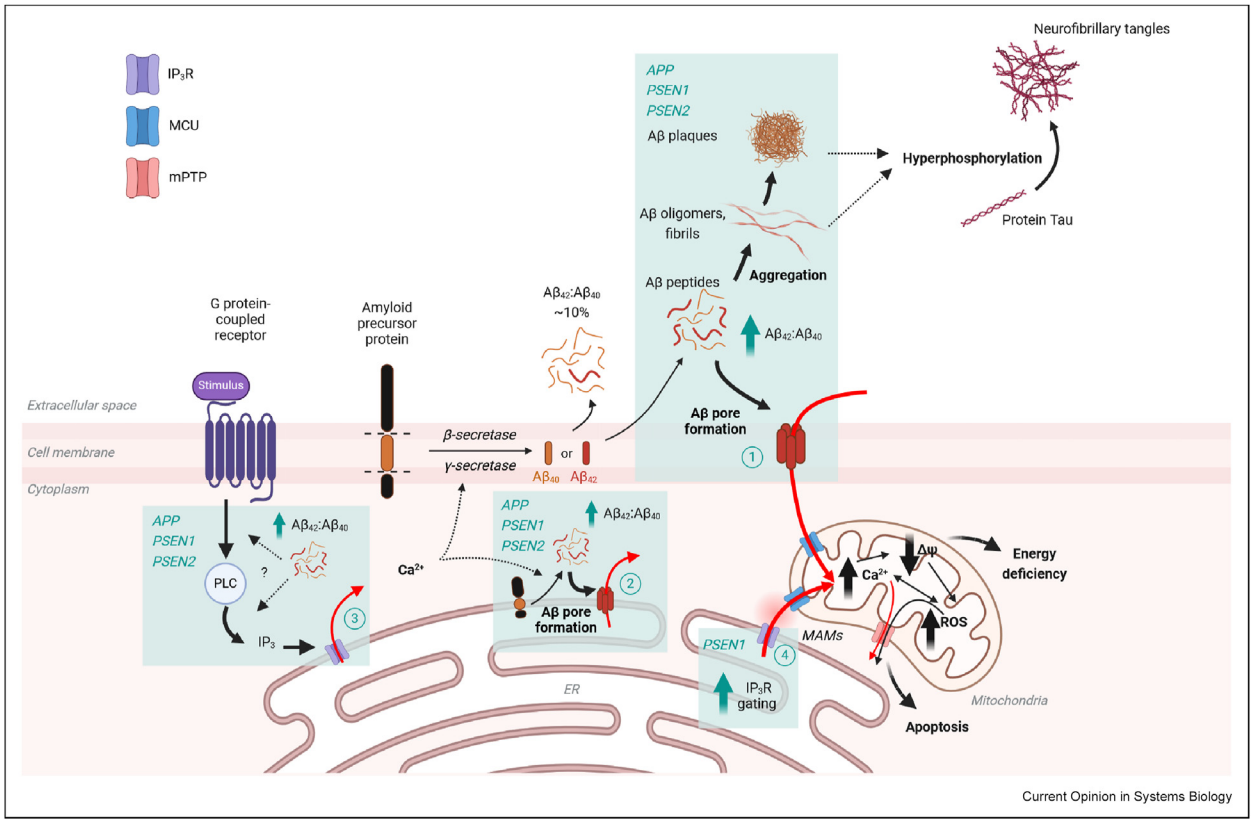
AD models

Familial and sporadic AD are both characterised by abnormal Aβ accumulation [3]. The cleavage of amyloid precursor protein (APP) by the β- and γ-secretase complexes releases Aβ peptides and takes place predominantly in the plasma membrane, ER and Golgi network [43]. In familial AD, mutations in genes coding for the APP or part of the γ-secretase complex enhance the formation of protein deposits, including Aβ plaques and neurofibrillary tangles [1,3] (Figure 2).

These mutations are responsible for many other pathological phenomena including impaired Ca^{2+} signalling [3,44]. Recent therapeutic strategies consider the so-called "Ca^{2+} hypothesis" and its tight connection to energy deficiency as a complementary view to the canonical amyloidogenic pathway [45]. Perturbations in Ca^{2+} dynamics arise very early in AD development, preceding the appearance of extracellular amyloid deposits and resulting most likely from *intracellular* Aβ dyshomeostasis [46,43], although amyloid-independent mechanisms have also been identified [47] (Figure 2). Of note, a PSEN1 mutation seems to increase the opening probability of IP_3Rs in an Aβ-independent way [48]. Intracellular Aβ increases cytosolic Ca^{2+} levels by inducing ER release through $Aβ_{42}$ pores formed in the ER membrane [49] or stimulation of IP_3Rs by Aβ-enhanced production of IP_3 [50,49], which perturbs the Ca^{2+} fluxes of other intracellular organelles such as mitochondria [51]. Additionally, pore-forming assemblies of extracellular Aβ in the plasma membrane (PM) enables large influx of extracellular Ca^{2+} [52]. Since Aβ production is itself modulated by Ca^{2+}, Aβ and Ca^{2+} are mutually activating their production and the resulting feedforward loop eventually causes neurodegeneration [44]. Moreover, mitochondrial Aβ accumulation decreases the activity of complexes III and IV in the ETC, leading to mitochondrial dysfunction and ROS accumulation [43].

In computational models, these AD-related perturbations can be incorporated in the description of cytosolic Ca^{2+} dynamics (Table 1). Several gating models, predicting the opening probability of IP_3Rs and the associated Ca^{2+} release from the ER, have been established based on experimental Ca^{2+} traces. Regardless of the exact mechanism rising cytosolic Ca^{2+}, cytosolic Ca^{2+} traces feed a bioenergetic model that predicts the evolution of key mitochondrial variables such as Ca^{2+}, ATP, NADH and ROS concentrations, and mitochondrial membrane potential. Cortassa's bioenergetic model [53,54] is widely used and accounts for the production of ATP through the TCA cycle and OXPHOS, and includes details of enzyme regulation - notably, the regulation of isocitrate dehydrogenase and α-ketoglutarate dehydrogenase by Ca^{2+}. This model also incorporates the anaplerotic reaction catalysed by aspartate transaminase, ROS generation by the respiratory chain and ROS scavenging. Overall, the computational models indicate that abnormal Ca^{2+} elevations affect the energy metabolism and ROS production by inducing mitochondrial Ca^{2+} overload and mitochondrial depolarisation, which in turn decreases the proton motive force driving the synthesis of ATP [55,51,56,57]

Figure 2



Ca^{2+} fluxes directly or indirectly associated with AD-related mutations leading to energy deficiency and apoptosis. The canonical pathway of APP cleavage by β- and γ-secretases yields a mixture of Aβ monomers of 40 or 42 residues with an $Aβ_{42}$:$Aβ_{40}$ ratio of about 10 %. In the presence of autosomal dominant inherited mutations of *APP*, *PSEN1* or *PSEN2* genes, APP cleavage generates a higher fraction of $Aβ_{42}$ which tend to aggregate into oligomers, fibrils and plaques. The metabolism of protein tau is altered by these aggregates, which leads to the assembly of neurofibrillary tangles. These mutations also remodel Ca^{2+} by favouring the formation of pores in the plasma membrane (1) or ER membrane (2), by enhancing IP_3-mediated stimulation of IP_3Rs (3) or increasing the open probability of IP_3Rs (4). Mitochondria take up these excess amounts of Ca^{2+}, which decreases the mitochondrial membrane potential (Δψ). ROS production is enhanced by Ca^{2+} overload and decoupling of OXPHOS, which decreases ATP synthesis and leads to energy deficiency - the details of the energetic perturbation cascade can be found in Figure 1. Finally, high intramitochondrial levels of ROS and Ca^{2+} trigger the opening of the mitochondrial transition pore (mPTP) and the release of apoptotic signals. (Red and black dashed arrows represent Ca^{2+} fluxes and direct activation of another process, respectively.)

(Figure 2). Additionally, the model of Toglia and Ullah shows that the spatial configuration of the MAMs modulates the opening probability of the mPTP, which also controls mitochondrial metabolism and apoptosis [51].

Ca^{2+} and metabolic remodelling affects non-neuron cells, as exemplified by the reactive astrocytes and activated microglia observed in the neighbourhood of plaques and tangles [7]. Under some conditions, astrocytes provide energy support to neurons in the form of lactate supply (astrocyte-neuron lactate shuttle) [15]. As shown with a spatio-temporal model of glucose metabolism, reactive astrocytes exposed to metabolic AD-related perturbations exhibit globally reduced ATP:ADP ratio and lactate export rate, which points to ATP deficiency and poor energetic support to neurons [61]. Interestingly, the morphological adaptation of the reactive astrocyte could locally mitigate the effects of AD-associated metabolic alterations in these cells due to limited transport in the ramified processes [61]. This hypothesis should be further investigated with a refined energy metabolism model and in a more specific context (synaptic transmission, neuroinflammation, Ca^{2+} signalling *etc.*) since the reactive transformation of astrocytes is shaped by the nature of the trigger [62]. The comprehensive and astrocyte-specific model of Latulippe *et al.* could for instance be incorporated to account for the Ca^{2+}-Aβ interplay [59]. How metabolites are spatially distributed through the cell or within brain tissue and how intercellular interactions perturb these profiles remain largely open questions that could be addressed with metabolic models of high spatio-temporal resolution.

Table 1

Computational models capturing the effects of AD on Ca^{2+} homeostasis and/or energy metabolism.

Ref	AD perturbation	Cytosolic Ca^{2+} handling	Metabolism	Energy measure	Spatial model	Other model assumptions
Mak et al.2015 [58]	Enhanced IP_3R gating by PS mutations	IP_3R gating model fitted to exp. data from Sf9 cells expressing mutant PS1	–	–	3D reaction-diffusion model	Opening of IP3Rs (stochastic) and Ca^{2+} release (deterministic). Ca^{2+} buffering by dye (deterministic).
Toglia et al. 2016 [55]	Enhanced IP_3R gating by PS mutations	Exp. Ca^{2+} traces from lymphoblasts of AD patients expressing mutant PS1	TCA cycle, OXPHOS, ROS [53,54]	[ATP]	–	–
Toglia et al. 2016 [51]	Enhanced IP_3R gating by PS mutations	IP_3R gating model and parameters from Mak et al. 2015 [58]	TCA cycle, OXPHOS, ROS [53,54]	[ATP]	**Ca^{2+} in MAMs**: reaction-diffusion model (Ca^{2+} flux through IP_3Rs + endogeneous buffering). **Whole-cell model**: non-spatial. Mitochondrial Ca^{2+} fluxes (MCU, NCX, mPTP) depend on Ca^{2+} level in MAMs	–
Toglia et al. 2018 [56]	$A\beta_{42}$-enhanced IP_3 production	IP_3R gating and whole-cell models fitted to exp. data from *Xenopus* oocytes	–	[ATP]	**Fitting of Ca^{2+} traces**: reaction-diffusion model. **Mitochondrial metabolism**: non-spatial.	Ca^{2+} exchanges with ECS neglected. Exogenous cytosolic Ca^{2+} buffering.
Latulippe et al. 2018 [59]	$A\beta$-enhanced Ca^{2+} entry. ($A\beta$ pores in PM) and sensitivity of RyR	IP_3R gating and whole-cell model	–	–	–	Astrocyte-specific. Detailed model of cell membrane potential dynamics. Ca^{2+} exchanges with ECS (PMCA, leak, VGCC). RyR. Module for IP_3 metabolism. Mitochondrial exchanges and metabolism neglected.
Minicucci et al. 2021 [60]	$A\beta$-enhanced IP_3 production	Whole-cell model fitted to exp. data from *Xenopus* oocytes	TCA cycle, OXPHOS, ROS [53,54]	–	–	Module for IP_3 metabolism. Mitochondrial exchanges and metabolism neglected. Ca^{2+} exchanges with ECS neglected.
Pensalfini et al. 2022 [57]	Brain extract-enhanced IP_3 production	IP_3R gating and whole-cell models fitted to exp. data from *Xenopus* oocytes (approach similar to Toglia et al. 2018)	–	[ATP]	**Fitting of Ca^{2+} traces**: reaction-diffusion model. **Mitochondrial metabolism**: non-spatial.	Ca^{2+} exchanges with ECS neglected.

Farina et al. 2023 [61]	Morphological changes in astrocytes (based on images from *post mortem* AD patient brains)	–	Glycolysis, TCA cycle, OXPHOS, LDH	ATP:ADP, lactose export rate	Reaction-diffusion model. Includes exp. astrocytic morphologies.	Astrocyte-specific. Spatially localised. enzymes. Coarse-grained metabolic kinetics (e.g. no enzyme regulation, mass action law kinetics for entire complex pathways).

PS – presenilin, RyR – ryanodine receptor, mPTP – mitochondrial transition pore, LDH – Lactate dehydrogenase, ECS – extracellular space, VGCC – voltage-gated Ca^{2+} channel.

Challenges and future directions

Towards a thermodynamically consistent description

In most models of brain energetics, the concept of energetic cost/production remains loosely defined. Absolute ATP concentration, ATP:ADP ratio, ATP consumption rate per surface or volume, or lactate export rate have been reported, which makes model comparison quite difficult. The energy systems approach proposed by Wellstead and Cloutier [16] paves the way to a more systematic approach. A next step would be to normalise those costs with respect to the basal energy input provided to cells in the form of oxygen, mitochondrial substrate, *etc.* The obtained *thermodynamic efficiency* would then become independent of the energy currency and capture the actual bioenergetic work performed by cells. Based on topological analysis and nonequilibrium thermodynamics, our recent study estimated the thermodynamic efficiency of mitochondrial metabolism regulated by Ca^{2+} for different cell stimulation and mitochondrial substrate levels [63]. Using similar frameworks in bioenergetics would for example avoid bias in estimations of energy deficiency induced by the decreased food intake in patients with neurodegenerative diseases. More generally, a unifying bioenergetic approach is necessary to rationalise the mechanisms connecting metabolic rewiring to the energetic demands and expenses, which are ubiquitous in neurodegenerative processes.

From sub-organellar to systems scales

In the reviewed kinetic models, most extracellular pathways as well as the dynamics of the intramitochondrial structures supporting ATP synthesis were overlooked. However, the internal structures of mitochondria, and more particularly cristae, can remodel in dependence on the matrix Ca^{2+} content, which affects the ATP synthesis capacities [64]. More or less sophisticated models enable to investigate the mechanisms of mitochondrial network adaptation due to fusion, fission, fragmentation and migration [22], while accounting for the ATP-dependency of these processes [65] or providing spatially resolved predictions in line with experimental data [66]. Even though mitochondrial adaptation proceeds on a different timescale compared to carbon metabolism or Ca^{2+} signalling (which is also a regulator of mitochondrial transport), a multiscale spatio-temporal framework could provide a more realistic description of energy delivery mechanisms. Intercellular exchanges, especially in the context of astrocytes and microglia activation, seem to significantly affect resource availability. With the growing interest for immunometabolism, the field of integrative bioenergetics should also witness the emergence of more models accounting for microglial involvement [14] and neuroinflammatory pathways.

Translational approaches based on mechanistic modelling remain scarce, but a recent attempt to connect molecular and cellular responses to motor skills succeeded in reproducing the symptomatic behaviours associated with PD and their improvement under medication with levodopa [67]. The model also offers clinical perspective by predicting the optimal level of levodopa to be administered in dependence on observed cell loss [67].

How impaired energetics and Ca^{2+} signalling are linked and contribute to neurodegeneration becomes more and more evident, highlighting the therapeutic potential of interventions targetting Ca^{2+} pumps and channels [45]. Nevertheless, many details still remain elusive and experiments guided by mechanistic modelling offer promising possibilities to unravel the underlying mechanisms of neurodegeneration.

Declaration of competing interest

None.

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Data availability

No data was used for the research described in the article.

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